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# The Economic Burden of Opioid Poisoning in the United States and Determinants of Increased Costs in Opioid Poisoning

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# THE ECONOMIC BURDEN OF OPIOID POISONING IN THE UNITED STATES AND DETERMINANTS OF INCREASED COSTS IN OPIOID POISONING

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University

by

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**Dedication:**

This dissertation is dedicated to my late grandmother, “Lola Ising”, whose high hopes for the grandson she raised have finally been realized. I love you, Lola.

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First and foremost, I would like to acknowledge God, through which I have derived the preservence necessary to succeed in the graduate program. I can do all things through Christ who strengthens me (Philippians 4:13).

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| | |
|---|---|
| ADE: | Adverse drug event |
| ADR: | Adverse drug reaction |
| AIDS: | Acquired Immune Deficiency Syndrome |
| ANOVA: | Analysis of variance |
| AWP: | Average wholesale price |
| CCI: | Charlson comorbidity index |
| CCR: | Cost-to-charge ratio |
| CDC: | Centers for Disease Control and Prevention |
| CHF: | Congestive heart failure |
| CI: | Confidence interval |
| CMS: | Centers for Medicare and Medicaid Services |
| CNS: | Central nervous system |
| CPI: | Consumer price index |
| CPT: | Current Procedural Terminology |
| DAWN: | Drug Abuse Warning Network |
| DPV: | Daily production value |
| DRG: | Diagnosis related group |
| DSM: | Diagnostic Statistical Manual for Mental Disorders |
| ECI: | Employment Cost Index |
| ED: | Emergency department |
| FDA: | Food and Drug Administration |

| | |
|---|---|
| FP: | For profit |
| HCUP: | Healthcare Cost and Utilization Project |
| HIV: | Human Immunodeficiency Virus |
| ICD: | International Classification of Diseases |
| ICU: | Intensive care unit |
| IQR: | Interquartile range |
| LOS: | Length of stay |
| NEDS: | National Emergency Department Sample |
| NFP: | Not for profit |
| NIDA: | National Institute on Drug Abuse |
| NIS: | National Inpatient Sample |
| NOS: | Not otherwise specified |
| NPV: | Net present value |
| NSDUH: | National Survey on Drug Use and Health |
| NVSS: | National Vital Statistics System |
| OLS: | Ordinary least squares |
| OR: | Odds ratio |
| PK: | Pharmacokinetic |
| PD: | Pharmacodynamic |
| QIC: | Quasi-likelihood under the independence model criterion |
| REMS: | Risk Evaluation and Mitigation Strategies |
| RxO: | Prescription opioid |
| SAMHSA: | Substance Abuse and Mental Health Services Administration |

| | |
|---|---|
| SD: | Standard deviation |
| SE: | Standard error |
| STI: | Sexually transmitted infection |
| TEDS: | Treatment Episode Data Set |
| T&R: | Treat-and-release |
| VHA: | Veterans Health Affairs |

## Abstract

**Introduction:**

Opioid poisoning has been rapidly increasing in the past decade, and has been driven in large part due to increases in opioid prescribing. This has been accompanied by intervention efforts aimed at preventing and reversing opioid poisoning through naloxone prescription programs. Current literature have not quantified the economic burden of opioid poisoning. Understanding this information can help inform these efforts and bring light to this growing problem. In addition understanding various determinants of increased costs can help to identify the types of populations more likely to have greater costs.

**Main Objectives:**

The objectives are 1) to quantify the economic burden of opioid poisoning, 2) to evaluate differences in costs, LOS, and in-hospital mortality depending on opioid type, 3) to identify opioids most likely to result in hospitalization for opioid-related ED visits and 4) to determine differences in the odds of admission to various hospital admission categories with respect to opioid type.

**Methods:**

A cost-of-illness approach was used to estimate the economic burden of opioid poisoning. Direct costs and prevalence estimates were obtained from nationally representative databases. Other sources of direct costs were obtained from the literature. Indirect costs were measured using the human capital method. Differences in costs, LOS, and in-hospital mortality were measured through generalized linear models using the National Inpatient Sample in 2009 from the Healthcare Cost and Utilization Project. The Drug Abuse Warning Network database was

used to evaluate opioids most likely to result in hospitalization and to evaluate the likelihood of different opioids to cause admission into different types of hospital settings.

**Results:**

Opioid poisoning resulted in an economic burden approximately $20.4 billion dollars in 2009. Productivity losses were associated with 89% of this total. Direct medical costs were associated with $2.2 billion. Methadone was associated with the greatest inpatient costs and LOS, while heroin was associated with a greater likelihood of in-patient mortality compared to prescription opioids. Heroin, methadone, and morphine were associated with the greatest odds of hospitalization. Among admitted patients, methadone, morphine, and fentanyl were each associated with the greatest odds of ICU admission compared with other opioids.

**Conclusions:**

Opioid poisoning results in a significant economic burden to society. Costs, length of stay, in-patient mortality and the odds of hospitalization and admission type depend on the type of opioid involved. The results from this study can be used to inform policy efforts in providing interventions to reduce opioid poisoning and help focus efforts on populations at highest risk for increased costs.

# Chapter I:

## Section 1.1: Introduction

Increases in opioid prescribing have ushered in a period of increased misuse and abuse of opioid analgesics. This has also been accompanied by increases in opioid-related emergency (ED) visits and associated mortality that has significantly increased over the past decade. As opioid analgesics have become more accessible, the opportunity for adverse drug events associated with these agents has grown. Local efforts to prevent opioid poisoning and to reduce opioid poisoning related mortality have been implemented across the country. In such efforts, education is provided to patients and caregivers along with prescribed naloxone that friends or caregivers can use should an episode of opioid poisoning occur. Providing a national estimate for opioid poisoning can help to inform efforts in providing these initiatives and can aid in demonstrating the value of these programs.

Previous studies have quantified the economic burden of opioid analgesic misuse and abuse, but have not focused on opioid poisoning specifically. These studies have also not presented data in such a way that the costs associated with each episode of poisoning can be estimated. This study fills the gap in the literature by providing such estimates using nationally representative data. Secondly, differences in inpatient hospital costs, length of stay, and in-hospital mortality were evaluated between broad opioid categories (heroin, methadone, non-methadone opioid analgesics). Finally, because of the high costs of hospitalization, specific opioids were evaluated for their likelihood to result in hospitalization among those who present to the ED as a result of opioid use. As differences exist in costs with regards to the type of

hospitalization, this outcome is also evaluated among admitted patients with respect to specific opioids.

The specific aims, hypotheses, introduction, and background are provided in this chapter. Chapter 2 provides a literature review regarding previous studies that have evaluated the costs of opioid misuse and abuse, along with the relevant conceptual frameworks that serve as a basis for this analysis. Chapters 3, 4, and 5 provide the methods, results and discussion for Specific Aims I, II, and III, respectively. Finally Chapter 6 contains the final conclusions given the findings for each of the specific aims.

## Section 1.2: Specific Aims

Specific Aim I:

A: Estimate the total yearly direct and indirect costs of opioid poisoning in the United States for heroin and prescription opioids.

B: Estimate the cost per poisoning event in the United States for heroin and prescription opioids.

C: Estimate the total direct and indirect costs for opioid poisoning caused by specific prescription opioids in the United States.

Specific Aim II:

A: Describe patient and hospital characteristics for inpatient stays involving heroin, methadone, and non-methadone opioid analgesics.

B: Evaluate differences in costs, length of stay and death between hospital stays for poisonings involving heroin, methadone, and non-methadone opioid analgesics.

Specific Aim III:

A: Describe patient characteristics among emergent opioid-related emergency department visits.

B: Identify opioids that are most likely to result in hospitalization among emergent opioid-related ED visits.

C: Among admitted patients, evaluate differences in ICU admission, psychiatric/detoxification admission, and transfers compared to other admissions for all opioids.

## Section 1.3: Hypotheses

These hypotheses are specific to Specific Aim IIA. Because of the potential differences in pharmacological properties between heroin and opioid analgesics and potential differences in demographic and behavioral characteristics between these populations, it was of interest to formally test differences in costs, length of stay, and in-hospital mortality between these agents.

1. Costs:
    a. Costs associated with inpatient treatment of opioid poisoning are highest for methadone compared with heroin or non-methadone opioid analgesics.
    b. Non-methadone opioid analgesics result in higher inpatient treatment costs than heroin.
2. Length of stay:
    a. The length of stay associated with inpatient treatment of opioid poisoning is highest for methadone compared with heroin or non-methadone opioid analgesics.
    b. Non-methadone opioid analgesics result in higher hospital length of stay than heroin.
3. In-hospital mortality:
    a. In-hospital mortality is more likely for methadone compared with heroin or non-methadone opioid analgesics.
    b. Non-methadone opioid analgesics result in a higher likelihood of in-hospital mortality compared with heroin.

## Section 1.4: Background

*Pharmacology*

Opioids are a class of biologically active substances that primarily affect the central and peripheral nervous systems through the binding of opioid receptors. Different types of opioid receptors exist in the body and are responsible for attenuating the perception of pain along with a host of other effects on the body, depending on the types of receptors involved. The three classical opioid receptors are the mu, kappa, and delta receptors.[1] Though all three are responsible for the analgesic effects, most of the clinically used opioids are selective for the mu receptor.[1] In sufficiently high doses, however, these opioids can interact with other receptor subtypes. The mu receptor is also responsible for other effects on the body, such as euphoria, physical dependence, miosis, decreased gastrointestinal motility, and respiratory depression.

Opioids have distinct pharmacokinetic and pharmacodynamic profiles. The prototypical opioid analgesic is morphine, originally derived from the opium poppyseed plant. As the prototypical agent, the potency of other opioids is measured relative to the potency of morphine. For example, fentanyl is one of the most potent opioid analgesics clinically used with a relative potency of 80.[1] Other opioids such as hydrocodone and codeine are less potent than morphine, with potencies of 0.6 and 0.2, respectively.[2] These opioids may also differ also in their elimination half life, which can depend on the intrinsic properties of the opioid and on the formulation. Opioids with extended half lives are considered "long-acting" opioid analgesics, as opposed to the "short-acting" opioids. The potencies and duration of action for these agents can have clinical implications on the appropriate use of these drugs in various populations, the abuse potential, and the development of adverse effects.

*Treatment of Pain*

Opioid analgesics are an indispensable treatment modality for the treatment of pain. These agents can be used to treat acute pain, chronic musculoskeletal pain, and cancer-related pain. The prevalence of chronic pain among adults has been found to vary between 2% to 40%.[3] In the United States, it has been estimated that approximately 31% of the population have chronic pain that persists for 6 months or more.[4] Among patients starting long-term opioid therapy for chronic non-cancer pain, back pain and extremity pain are the most common pain diagnoses (38% and 30%, respectively).[5] Other less common pain diagnoses include osteoarthritis, neck pain, abdominal pain, headache, and menstrual pain.[5] The most commonly prescribed opioid analgesics in chronic non-cancer related pain are hydrocodone and oxycodone (46% and 25%, respectively).[5]

The goals for the treatment of chronic pain include management of the symptoms of pain and improved physical and/or psychosocial function.[6] Despite the wide use of opioids in chronic non-cancer related pain, the evidence for the effectiveness and safety of these agents in this setting is less compelling. Evidence from short-term ($\leq$12 weeks) clinical trials suggests that opioids are moderately effective for pain relief and only slightly effective for improved functional outcomes.[7] The evidence for the long-term use (> 6 months) of opioids in chronic noncancer pain is sparse.[7] When evaluating the use of opioids specifically for chronic low back pain, the evidence is even less supportive. A recent systematic review concluded that opioids are no more effective than non-steroidal anti-inflammatory drugs (a.k.a., NSAIDs) for the treatment of chronic low back pain and that their use confers a greater incidence of adverse effects.[8]

The role for opioids in cancer-related pain is clearer. Opioid analgesics are a mainstay in the treatment of mild to moderate cancer-related pain in non-palliative and palliative settings.

Guidelines incorporate the rational use of opioids for this population in treating pain. For example, the World Health Organization advocates a three-step approach to addressing cancer pain, starting with non-opioids as an initial step, mild opioids such as codeine with or without non-opioids for mild symptoms that continue to persist, and then strong opioids for moderate to severe pain.[9]

Uncontrolled pain results in significant morbidity, healthcare costs, and lower quality of life.[10, 11] Though pain is one of the most common reasons patients see physicians, it has been historically undertreated. This was thought to be due to inadequate education, legal and regulatory pressures, concerns regarding side-effects, physicians' perceptions regarding the validity of patient's complains of pain, among other reasons.[12] Other frameworks suggest that the undertreatment of pain results from the subjectivity of pain, a poorly understood causal basis of pain, and the perception of pain as only a symptom rather than a disease.[12] Nevertheless, improvements have been made, with increased recognition for the need for optimal pain management. In January 1, 2001, Congress passed into law a provision that declared it the start of the Decade of Pain Control and Research.[13] This has helped in efforts to bring greater awareness to the need for pain control and in developing programs that address the treatment of pain. Consequently, changes in practice guidelines have advocated for adequate pain control while recognizing the potential for addiction, misuse and abuse. This presents physicians with the challenge of adequately treating pain while ensuring that they avoid the risk for subsequent misuse and abuse of the opioids.

*Definitions of Misuse and Abuse*

It is important to understand the contexts under which opioid poisoning may occur. Misuse, abuse, and dependence are terms often used that describe behaviors related to opioid use disorders. In addition, opioid poisoning may be due to iatrogenic causes, such as prescribing an inappropriately high dose or other medications that may interact with the opioid analgesic. Underlying substance dependence or addiction may have an effect on drug-seeking behaviors that contribute to opioid misuse or abuse. The terms "dependence" and "addiction" have been used interchangeably in the literature, and for the purpose of this dissertation, are synonymous. Definitions are summarized in Figure 1.1. Dependence is defined by the Diagnostic Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) as "a maladaptive pattern of substance use leading to clinically significant impairment or distress" within a 12-month period with signs of tolerance, withdrawal, drug-seeking behaviors, and other factors that represent an impediment of social functioning.[14] The DSM-IV defines substance abuse as "a maladaptive pattern of substance use leading to clinically significant impairment or distress" within a 12-month period with specified substance-use related behaviors that adversely impact different types of measures of day-to-day functioning that is not preceded by dependence.[15] This definition treats substance abuse as a separate disorder from substance dependence. However, the distinction between the two has been called into question by several studies and developing DSM-V criteria call for removing the distinction between abuse and dependence when defining opioid use disorders.[16] It is important to note that the DSM-IV criteria define these disorders in terms of long-term, behavioral patterns and can be difficult to apply on an episodic basis. For example, an individual that consumes the drug one time for the purposes of getting high (i.e., non-medical use, or abuse) would not meet the psychiatric definition of a substance abuser.

Other definitions have been used to describe aberrant drug use behaviors on an episodic basis. Prescription drug misuse is defined by the National Institute on Drug Abuse (NIDA) as "taking a medication in a manner other than that prescribed or for a different condition than that for which the medication is prescribed" and drug abuse as "the intentional misuse of a medication outside of the normally accepted standards of use."[17] Using this definition, prescription drug abuse can be considered a subset of prescription drug misuse. Misuse has also been defined as the "use of a medication (for a medical purpose) other than as directed or as indicated, whether willful or unintentional, and whether harm results or not" and abuse as "any use of an illegal drug" or "the intentional self-administration of a medication for a nonmedical purpose such as altering one's state of consciousness."[18] Though these definitions are more amenable for characterizing illicit drug use on an episodic basis, they require detailed information regarding the circumstances of the use of the drug to correctly distinguish between misuse and abuse.

*Use of Opioid Analgesics*

The increased recognition for the adequate treatment of pain has ushered in a period of rapid increases in utilization. From 1992 to 2001, the use of opioids increased from 43 per 1,000 patient visits to 59 per 1,000 patient visits.[19] From 1995 to 2004, prescribing for various opioids increased by as much as close to 3-fold over the time period.[20] Though this increase reflects increased access to opioid analgesics in the treatment of pain, it has not been without harm as increases in misuse and abuse of these agents have been noted. From 1995 to 2004, self-reported non-medical use and drug-related emergency department visits for these drugs increased by 6.4- and 5.6-fold, respectively, for oxycodone.[20] Increases in opioid poisoning mortality have also

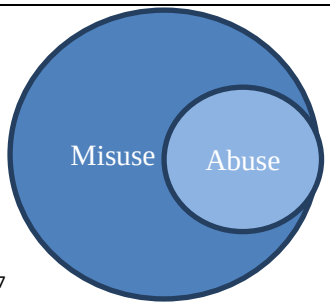
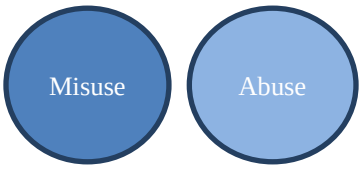
been documented in the past decade. Evidence exists that sales, overdose death rates, and substance abuse treatment admissions increased in parallel from 1999 to 2008.[21] In the past decade, opioid poisoning mortality has increased by as much as 3-fold.[22] Root causes for opioid poisoning mortality have been found in part to be due to physician error, knowledge deficits, patient non-adherence, and unanticipated medical and mental health comorbidities.[23]

*Use of Heroin*

It has been estimated that 620,000 Americans used heroin at any point in 2011. This is in contrast with non-medical prescription opioid use (i.e., prescription opioid abuse) in the same year, which was estimated to be 11,143,000.[24] The disparate use of heroin compared to prescription opioid analgesics also translates to fewer deaths compared to the latter. Heroin related deaths have remained steady from 1999 through 2007, with approximately 2,000 deaths in 2007, compared to just under 12,000 deaths for prescription opioids in the same year.[25]

Heroin users represent a distinct population compared to misusers and abusers of prescription opioid analgesics. For example, a relatively large percentage of heroin users have HIV/AIDS (up to 3.4%) or hepatitis (up to 27.5%) and are 2.8 and 6.4 times as likely as nonusers to have these conditions, respectively.[26] This is due to not only riskier behaviors that these users engage in but can be attributed to the common method of administering heroin via injection. Furthermore, the use of heroin is limited to only those who use the drug non-medically (and can be solely classified as a street drug), while prescription opioid use can occur among medical and non-medical users.

**Figure 1.1: Misuse, Abuse and Dependence Definitions**

| Definition Source | Definition | |
|---|---|---|
|  NIDA[17] | Misuse: | "Taking a medication in a manner other than that prescribed or for a different condition than that for which the medication is prescribed." |
| | Abuse: | "The intentional misuse of a medication outside of the normally accepted standards of use." |
| Katz et al. [18]  | Misuse: | "Use of a medication (for a *medical* purpose) other than as directed or as indicated, whether willful or unintentional, and whether harm results or not." |
| | Abuse: | "Any use of an illegal drug" or "the intentional self-administration of a medication for *a nonmedical* purpose such as altering one's state of consciousness." |
| DSM-IV[15]  | Dependence: | "a maladaptive pattern of substance use leading to clinically significant impairment or distress" within a 12-month period with signs of tolerance, withdrawal, drug-seeking behaviors, and other factors that represent an impediment of social functioning." |
| | Abuse: | "a maladaptive pattern of substance use leading to clinically significant impairment or distress" within a 12-month period with specified substance-use related behaviors that adversely impact different types of measures of day-to-day functioning that is not preceded by dependence." |

*Presentation and Treatment of Opioid Poisoning*

The presence of hypopnea or apnea, miosis, and stupor, in combination with an assessment of patient history can lead to a diagnosis of opioid overdose.[27] Though the classic

toxidrome may include apnea, stupor, and miosis, the clinical presentation of opioid poisoning may involve of a variety of other findings (Table 1.1). These three types of symptoms may not be consistently present in all cases. Respiratory depression (defined as 12 breaths per minute or less) can be potentially life threatening if not treated. Decreased respiratory rate has been shown to be most predictive of opioid poisoning, and results in decreased oxygen saturation and subsequent coma and death.[28] Most cases of opioid poisoning can be managed in the emergency department, with more severe or complicated cases requiring inpatient admission. Patients with apnea may require pharmacologic or mechanical stimuli for respiration.[27] For patients with stupor and who have respiratory depression, ventilation is provided. Pharmacologic treatment consists of naloxone, a competitive mu receptor opioid antagonist, to reverse the CNS depressant effects of the offending opioid. It is usually administered in the hospital setting, but can be given by emergency medical service personnel in some settings. Subcutaneous, intramuscular, and intravenous formulations exist, but intranasal administration has been described as generally effective and safe in the literature. In most cases, the administration of naloxone can completely reverse all symptoms, but complications such as persistent hypoxemia, pulmonary edema, compartment syndrome, and rhabdomyolysis may occur. Some patients may require multiple dosing or continuous infusions of naloxone, especially in cases where symptoms are persistent and/or a long acting drug was administered. Certain populations, such as children and the elderly, may have prolonged toxic effects and unexpectedly severe poisoning, necessitating closer monitoring.[27]

**Table 1.1: Clinical Presentation of Opioid Poisoning**[27]

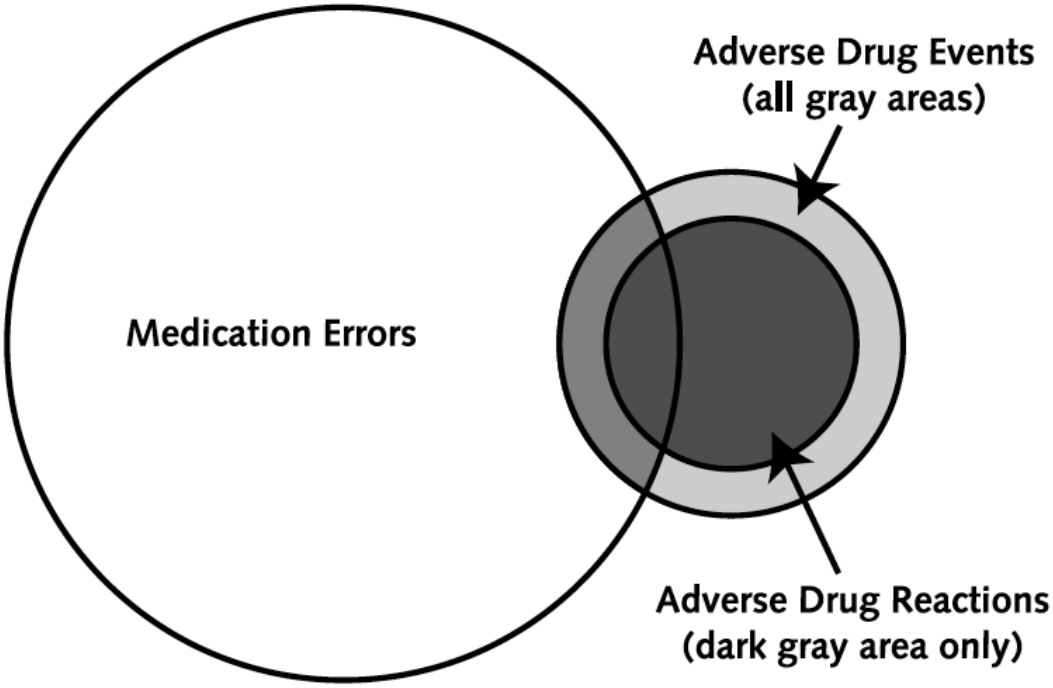
1. Respiratory depression
2. Miosis
3. Stupor
4. Hepatic injury from acetaminophen or hypoxemia
5. Myoglobinuric renal failure
6. Rhabdomyolysis
7. Absent or hypoactive bowel sounds
8. Compartment syndrome
9. Hypothermia
10. Possible presence of one or more fentanyl patches

*Opioid Poisoning as an Adverse Drug Event*

Misuse and abuse of opioids can result in a reduced ability to function normally in society and can carry criminal and legal consequences. Because misuse and abuse occur outside standard uses, it can increase the likelihood of opioid poisoning. Opioid poisoning can be thought of as falling under several categories of drug events. An adverse drug event (ADE) is defined as an "injury resulting from the use of the drug".[29, 30] An adverse drug reaction (ADR) is defined as a "harm directly caused by a drug at normal doses".[29, 31] In this respect, ADRs are considered a subset of ADEs. A medication error is defined as "inappropriate use of a drug that may or may not result in harm" and a side effect is a "usually predictable or dose-dependent effect of a drug that is not the principal effect for which the drug is chosen".[29]

Opioid poisoning can be considered as an injury from the use of a drug (i.e., ADE), but can potentially occur at normal, therapeutic doses as well (i.e., ADR). It may also be the effect of a medication error in cases where the opioid was misused or abused. Other common ADRs associated with the use of OAs include nausea, vomiting, constipation, and sedation.

**Figure 1.2:**
**Relationship of Adverse Drug Events, Adverse Drug Reactions, and Medication Errors[29]**




*Interventions for Opioid Misuse, Abuse, and Poisoning*

Regulatory action has also been established to ensure that these drugs are prescribed and used safely. For example, Risk Evaluation and Mitigation Strategies (REMS) have been implemented for various opioid analgesics. The requirement for REMS for drugs with known or suspected risks of abuse or overdose was established as part of the FDA Amendments Act of 2007. Since 2009, the FDA has implemented requirements for REMS from manufacturers for a variety of opioid products such as morphine, oxycodone, fentanyl, buprenorphine, among others. These strategies vary and may require a combination of the provision of a medication guide to patients, elements to assure safe use that can vary by drug, and an implementation plan. The FDA has also recently begun to focus more efforts into requiring REMS for longer-acting and extended release opioids due to an increased risk of overdose and death from the use of these

agents. Though REMS may reduce abuse of these drugs, empirical evidence for the effectiveness of REMS in reducing adverse events is lacking.

As another example, "prescription monitoring programs" exist at the state level and house databases that contain prescriber and patient-level prescription data on drugs of abuse. These data are used in different ways depending on the state. In most states, information is provided to pharmacy and other healthcare professionals and in some, can be provided to law enforcement or Medicaid programs. These programs make this information available to healthcare professionals so that proper preventive and treatment efforts can be made to those that are identified as drug abusers and data show that these programs are effective in altering prescriber behavior.[32]

Though prescription drug monitoring programs and REMS are intended to promote the safe use of drugs and to deter abuse, other initiatives have been implemented that address opioid poisoning directly. These programs, akin to syringe exchange programs, supply naloxone as an outpatient prescription to be administered by a friend or family member to patients who are known abusers or at high risk of abuse. As cases of opioid overdoses have increased over the past decade, an increase in the number of such programs has been noted.[33] Several challenges to these programs have been cited including costs, training, and medical liability.[34] Despite these challenges, access to naloxone has the potential to save lives and reduce healthcare costs.

## Section 1.5: Rationale

Rates for prescription opioid misuse and abuse have been rapidly rising over the past decade and have been attributed in large part to rising rates of opioid prescribing.[20] Accordingly, rates of prescription opioid poisoning and related mortality have risen by as much as 3-fold since 1999, far outpacing that of illicit drugs such as cocaine and heroin [22] A growing number of initiatives across the nation have sought to prevent and reverse opioid poisoning through education and increasing access to prescription naloxone [33]

Though costs associated with misuse and abuse of prescription opioids have been well documented in the literature, most have not focused on costs specifically related to opioid poisoning.[35-39] Furthermore, previous studies have only evaluated prescription opioids and do not include heroin in their analysis. As initiatives, such as naloxone prescription programs, are targeted towards injection drug users with a growing focus on prescription opioid abusers,, evaluating the costs of both heroin and prescription opioid poisoning is worth considering.

Evaluating factors related to hospitalization and increased costs relating to hospitalization are important as inpatient costs are also likely to represent the largest component of direct medical costs in opioid poisoning. In 2010, inpatient hospital care represented approximately 33% of the $2.2 trillion in national health expenditures in the United States.[40] Indeed, hospital care is an expensive component of direct medical costs and evaluating factors that increase inpatient care costs or increase the likelihood of inpatient care can further elucidate which types of patients are more likely to be costly when experiencing opioid poisoning.

Therefore, in addition to quantifying the costs of opioid poisoning to society this dissertation also focuses on evaluating determinants of increased costs in terms of differences in

costs, length of stay, and mortality among opioid types after admission to the hospital. Patient and hospital characteristics are also described to characterize those patients who are admitted to the hospital for opioid poisoning. Also explored in this dissertation are differences in the hospitalization between opioid types and in different categories of hospital care, such as the intensive care unit (ICU). This was done to understand the severity in the varying presentations of opioid-related ED visits and the nature of hospitalization for these types of cases.

# Chapter II:

## Literature Review and Conceptual Framework

### Section 2.1: Systematic Literature Review on the Economic Burden of Opioid Poisoning

A systematic literature review was conducted in June 2012. MEDLINE, CINAHL, ECONLIT, and IPA were searched for the following terms: (“opiate” OR “opioid” OR “opiates” OR “opioids”) AND (“cost” OR “costs”) AND ("misuse" OR "abuse" OR "poisoning" OR "overdose" OR “intoxication” OR “dependence”). Titles and abstracts were first screened for inclusion criteria and exclusion criteria. After applying the exclusion criteria, article reference lists from included studies and review articles were evaluated for eligibility for inclusion in the literature review. The inclusion and exclusion criteria that were applied are defined as the following:

Inclusion criteria:

1. Evaluates costs attributed to opioid misuse, abuse, and/or poisoning

Exclusion criteria:

1. Does not evaluate the costs of prescription opioid use
2. Evaluates cost-effectiveness of opioid analgesics
3. Studies not conducted in the United States
4. Only evaluates costs associated with treatment dependence

The search over all databases yielded 496 articles. In addition, review articles were reviewed to search for other relevant articles that may have been missed in the literature search.[41-47] After eliminating duplicates and applying inclusion and exclusion criteria, a total of five original research articles were found.

**Table 2.1: Included Articles from Literature Review and Summary of Findings**

| Author | Opioid Use | Data Sources | Costs | Findings |
|---|---|---|---|---|
| White et al. [35] (2005) | "Abuse" | Administrative claims data | Direct | Abusers vs. Not ($15,884 versus $1,830, P < 0.01)* |
| McAdam-Marx et al.[39] | "Abuse and misuse" | Medicaid data | Direct | Poisoning vs. Not $16,952 versus $7,066; P < .001)* |
| Birnbaum et al. [36] (2006) | "Prescription opioid abuse" | NSDUH<br>TEDS<br>DAWN<br>Private claims data<br>Secondary data | Direct and indirect | $8.6 billion annually |
| Hansen et al. [38] (2011) | "Nonmedical use" | NSDUH<br>NVSS Mortality File<br>Other secondary data sources | Direct and indirect | $50 billion annually |
| Birnbaum et al. [37] (2011) | "Abuse, dependence and misuse" | Private claims data<br>Florida Medicaid<br>NSDUH report<br>Other secondary data sources | Direct and indirect | $55.7 billion annually |

*per patient, per year, total aggregated costs; NSDUH = National Survey on Drug Use and Health; TEDS = Treatment Episode Data Set; DAWN = Drug Abuse Warning Network

## Summary of Literature

### White et al.[35] (2005)

White et al.[35] evaluated the payer burden of opioid abuse using data from a large administrative claims database containing data on medical claims and prescription claims from approximately 2 million insured members from 16 large employers during the years 1998 through 2002. Abusers and non-abusers were compared during a 6 month post-index period during this time period. Opioid abusers were defined as those having an ICD-9-CM code for opioid dependence, combinations of opioid abuse with other, opioid abuse, and poisoning by opiates excluding heroin. Non-abusers were drawn from the same overall population and matched in a 3:1 ratio to abusers based on gender, age, employment status, and census geographic region. Non-abusers were defined as those who did not have an ICD-9-CM diagnosis of opioid dependence, opioid abuse or poisoning.

Medical utilization was categorized both by place of service and type of medical service. Places of service included outpatient physician visits, outpatient mental health visits, hospital inpatient stays, emergency room visits, mental health inpatient stays, and another category for "other" places of service. Medical services included motor vehicle traffic accidents, trauma, outpatient substance abuse treatment, inpatient substance abuse treatment, and mental disorders.

Abusers were found to have significantly greater utilization in each of the places of service and greater consumption of each of the medical service categories. Pain and non-pain comorbidities were also compared between abusers and non-abusers. A larger percentage of opioid abusers were found to have various pain diagnoses compared to non-abusers. Similarly, abusers had a greater percentage of various comorbidities compared to non-abusers. Such comorbidities included non-opioid poisoning, hepatitis, pancreatitis, psychiatric diagnoses, liver

disease, HIV/AIDS and other STDs, among other diagnoses. The total average aggregated per-patient direct healthcare costs were found to be $15,884 for opioid abusers and $1,830 for non-abusers ($p < 0.01$), representing a difference of $14,054 per patient. Hospital inpatient costs represented the greatest percentage of costs (48%), followed by physician visit/outpatient costs (34%), drug costs (13%) and "other" costs (5%, including other places of service and emergency department costs). The differences in cost do not take into account differences in comorbidities. In a sensitivity analysis, a multivariate regression was performed comparing opioid abusers to matched patients diagnosed with depression. Depression was chosen because it is common and diagnosed consistently, managed by primary care doctors and specialists, and is costly to payers. The investigators controlled for age, sex and comorbidities. In this analysis, the incremental cost of treating opioid abuse patients compared to depressed patients was $3,040 after controlling for comorbidities.

The goal of this study was to measure how much extra it costs to treat abusers vs. non-abusers. As such, it represented all types of healthcare expenditures.. Although the study accomplishes this goal, the primary analysis does not attribute the total differences in costs to opioid abuse since it did not control for comorbidities. In the sensitivity analysis, the authors were able to compare the incremental cost of opioid abusers to patients who were depressed after controlling for various comorbidities, but did not specifically measure the incremental costs directly attributable to the abuse treatment-related services (i.e., poisoning, detoxification) in a general population.

The authors also applied a liberal interpretation of opioid abuse by including patients who had diagnoses for dependence and poisoning. Different definitions exist for "abuse", including that given by NIDA, Katz, et al., and the Diagnostic Statistical Manual-IV (DSM-IV) as used in

psychiatry.[14, 15, 17] The DSM-IV distinguishes dependence as a separate condition from opioid abuse, and other definitions distinguish between misuse (i.e., unintentional use of a drug outside normal use, or for a medical purpose) and abuse (i.e., intentional misuse, or for a non-medical purpose). Whether patients had the intent to use the drug for recreational purposes or if the patient was simply overmedicating to adequately control pain was not considered. Poisoning is not necessarily exclusive to the abuse of the drug, but can be related to misuse as well.

This study did not distinguish between poisoning costs and other costs associated with abuse. It does, however, distinguish between "inpatient" costs and other costs. Inpatient costs can include patients who need to be monitored and hospitalized for dependence and abuse behaviors rather than for diagnoses directly related to poisoning. This study also used data from private employers and is not generalizable to the national population. Other populations with a lower socioeconomic status (i.e., Medicaid patients) may be predisposed to higher costs.[48-54] Finally, only direct costs were considered; indirect costs were not included in the analysis.

**McAdam-Marx et al.[39] (2010)**

McAdam-Marx et al.[39] performed a similar analysis in the Medicaid population. The data was taken from the Medicaid Analytic eXtract (MAX) files representing data from all 50 states and the District of Columbia. Patients were identified using the same ICD-9-CM codes used by White et al.[8] in the previous analysis. The index date was defined as the date of the first abuse-related diagnosis in 2002, after which a 12-month evaluation period followed. Non-opioid abusers were sampled from the same general population and were matched in a 3:1 ratio to opioid abusers based on age, gender, and state of residence. These control patients were defined as those who did not have a diagnosis of opioid abuse. All patients included in the study had to

have at least 12 months of continuous eligibility from January 1, 2002 through December 31, 2003. During the evaluation period, costs pertaining to prescription drug use and location of care were obtained. Pain and non-pain-related comorbidities were tracked as outcomes during the period. After costs were obtained, multivariate regression analyses were performed to control for patient demographics and differences in comorbidities.

It was estimated that the prevalence of opioid abuse and/or dependence was 8.7 per 1,000 Medicaid patients. Costs for opioid abuse/dependence patients were significantly higher than the matched control group, at $14,537 and $8,663, respectively, with a difference of $5,874. Patients with an opioid poisoning diagnosis had an overall excess cost of $9,886 over the entire year ($16,952 vs. $7,066). In the regression model, abuse patients were found to have a significantly greater total adjusted cost ($23,556 vs. $8,436). The most common comorbidities were psychiatric disorders (49%), pain-related diagnoses (49%) and substance abuse (45%). A higher proportion of abusers had HIV/AIDS compared to non-abusers. The relative risks for having particular comorbidities relative to matched controls were highest for those having experienced other non-opioid poisonings (7.7) and hepatitis A, B, or C (7.2). Odds ratios were highest for substance abuse (9.4), hepatitis A, B or C (8.8) and poisonings (8.5). In this analysis, different types of comorbidities that tend to be associated with substance abuse were controlled for, including psychiatric diagnoses, HIV/AIDS, various skin infections, liver disease, hepatitis, and other STDs.

Several limitations existed with this analysis. Results from this study cannot be generalized to the total population. Those from Medicaid come from a lower socioeconomic status compared to patients under private insurance plans. Another consideration is that no pre-index period requirement was placed on the sample. Patients may thus have been diagnosed with

an opioid use disorder or opioid poisoning prior to the given index date. Unlike in White et al., this study stratifies costs by diagnosis type. Thus, the cost 1-year after diagnosis of opioid poisoning was obtained. However, it cannot be determined from this analysis how much of these costs are directly attributed to the opioid poisoning event and no further information regarding specific resource utilization after this event was obtained. This is because annual yearly costs were measured as the total incremental costs for the entire year with no specification for the source of the increased costs. Furthermore, the figure obtained does not adjust costs related to opioid poisoning specifically, and only adjusted costs for comorbidities when evaluating all opioid abuse diagnoses together..

**Birnbaum et al.[36] (2006)**

The previous two studies focused on evaluating the per-patient cost of opioid abuse. The next studies focus on obtaining an overall annual estimate of opioid abuse in the United States. In the first such study, Birnbaum et al.[36] estimated the costs of prescription opioid abuse in an employed population and used two methods to obtain the estimate: 1) a "quantity" method (i.e., a bottom-up approach) whereby survey-derived prevalence estimates of reported opioid abuse are multiplied by the per-patient cost of abuse, and 2) an "apportionment" method (i.e., top-down approach) that starts with the overall drug abuse costs and apportions the total cost to opioid abusers based on the percent of opioid abusers among all drug abuse. Included in the total estimate were healthcare costs, criminal justice costs, and workplace costs.

Healthcare costs included treatment costs for substance abuse and excess medical costs excluding substance abuse treatment costs to avoid double counting. Treatment costs were estimated using the apportionment method using data from the Office of National Drug Control

Policy (ONDCP) in 2001 for the costs and the Treatment Episode Data Sets (TEDS) for the ratio of opioid abusers to total drug abusers. Excess medical costs were estimated using a privately insured administrative claims database. Opioid abusers were compared to non-abusers using a log-linear regression controlling for patient demographics, employment status, geographical location, insurance plan type, and the presence of particular pain-related comorbidities. Once the differences in costs were obtained through the regression, the quantity method was used by multiplying this per-patient difference by prevalence estimates of opioid abuse obtained from the National Survey of Drug Use and Health (NSDUH).

Criminal justice costs included costs related to police protection, legal and adjudication costs, and costs related to correctional facilities. The apportionment method was applied using several datasets and other publicly available data. Workplace costs included those from premature death, reduced wages and/or employment, and incarceration. Data for premature death were estimated using data obtained from the Drug Abuse Warning Network (DAWN). Associated costs using the human capital method were taken from data from the Current Population Survey and national Vital Statistics life tables data. The number of inmates for prescription opioid abuse offenses was multiplied by the gender-specific average earnings and employment rates.

Treatment costs and excess medical costs were summed to $126 million and $2.48 billion, respectively, with a total of $2.6 billion for healthcare costs. Criminal justice costs were estimated to be $1.4 billion. Premature death was estimated at $865 million, reduced wages at $3.0 billion and incarceration at $658 million for a total of $4.5 billion in total workplace costs. The total societal costs were estimated at $8.6 billion. All reported costs are reported in 2001 U.S. dollars.

Several limitations existed with this analysis. Treatment costs were not measured directly. Instead, a "top-down" approach (i.e., apportionment method) was used, and did not allow for direct measurement of treatment costs. This relies heavily on various assumptions and several calculations from multiple datasets to obtain a final estimate. Because of this, specific resources used (i.e., outpatient, inpatient, etc.) were not able to be measured and costs could not be attributed to specific reasons for utilization, whether for opioid dependence, poisoning, withdrawal, or other abuse-related diagnoses. Excess medical costs were measured between patient who were opioid abusers compared to those who were not. When this method was employed by White et al. [35], patients were matched based on certain characteristics. In this case, they were not. Another limitation is that these excess costs were not necessarily directly attributable to opioid abuse. Only pain-related diagnoses were controlled for in the analyses. This analysis does not establish whether or not comorbidities such as bloodborne pathogens and psychiatric comorbidities were directly related to the opioid abuse. Therefore, some of the excess medical cost per-patient may be overstated when attributing these costs to opioid abuse. Patients that engage in drug abuse may engage in behaviors that are riskier in general and may be more susceptible to particular comorbidities that are not directly a result of the actual drug use. While the final figure for direct medical costs would be helpful in determining how much this population costs to payers, it would be less useful for informing interventions designed to address specific components of opioid abuse such as opioid poisoning.

**Birnbaum et al. [37] (2011)**

In the most comprehensive analysis to date, Birnbaum et al.[37] conducted a subsequent analysis, updating previous estimates[36] by including caregiver burden, additional criminal justice and lost productivity costs, and a more comprehensive dataset to measure the prevalence of opioid mortality. Similar to the previous analysis by Birnbaum et al.[36], total costs consisted of three components: health care, criminal justice, and lost workplace productivity costs.

Healthcare costs were derived from excess medical and drug use, substance abuse treatment, prevention, and research. Excess medical and drug costs were measured using a privately insured administrative claims database and the Florida Medicaid database. The privately insured database contained information not only on opioid abusers, but that of caregivers in the same insurance plan as well. Three groups were used to evaluate costs: 1) the Florida Medicaid sample, 2) privately insured opioid abusers, and 3) caregivers of the privately insured abusers. Each group was matched 1:1 to controls on age, gender, geographic location, employment status (for privately insured), and race (Medicaid only). Controls for the opioid abusers were those that did not have a diagnosis of opioid abuse (irrespective of opioid use) and controls for caregivers were those who were not considered caregivers for opioid abuse patients. It was not clear how controls for caregivers were selected. The per-patient costs for each of the three groups was then multiplied by the prevalence of reported opioid abuse as reported through the NSDUH. Treatment, prevention, and research costs were calculated using the apportionment method (i.e., top-down approach) using overall costs for substance abuse for each of the categories and then subsequently multiplying by the ratio of opioids to overall drug abuse.

Criminal justice costs were calculated using the apportionment method and considered spending related to opioid abuse on police protection, legal and adjudication costs, correctional

facilities, and property lost due to crime. Data were obtained from the Criminal Justice Expenditures and Employment Extract Program (CJEEP) and was multiplied by the proportion related to opioid abuse for arrests or incarcerations.

Lost workplace productivity costs included absenteeism, presenteeism (i.e., reduction in productivity while working), incarceration, and premature death costs and were calculated using the human capital method. Per-patient absenteeism and disability costs were calculated using data from a privately insured administrative claims database and multiplied by the number of employees with opioid abuse. Presenteeism costs were measured using a ratio of total medical, drug, absenteeism, and disability costs. Lost productivity from incarceration was estimated using the per-inmate cost of incarceration and multiplied by the number of inmates incarcerated for crimes due to opioid abuse. Premature death was calculated using data from DAWN and multiplying by the average lifetime earnings by age and gender.

The total economic burden was calculated to be $55.7 billion in 2006 dollars. Healthcare costs consisted of approximately 45% of the total amount, or $25 billion. Of this amount, excess medical costs comprised 94.9% or $23.7 billion, with the rest consisting of substance abuse treatment and prevention/research. Costs for opioid abuse patients consisted of 92% of the excess medical costs, with the remaining attributed to caregiver costs. The Medicaid population consisted of one-third of all excess medical and drug costs and Medicare patients and caregivers accounted for about 5% of all excess costs.

Criminal justice costs accounted for approximately $5.1 billion. The greatest share of costs was represented by correctional facilities (44.1% of all criminal justice costs), followed by police protection (29.7%), legal and adjudication (14.1%) and property lost due to crime (12.2%). The largest of the three components of total costs was due to lost workplace

productivity, representing 46% of the total, or $25.6 billion. Of this, premature death contributed the largest percentage, or 43.8% or $11.2 billion. This was followed by lost wages/unemployment (31.0%), excess disability and medically related absenteeism (10.2%), presenteeism (8.0%) and incarceration (6.9%).

This is the first the study evaluating costs related to opioid abuse incorporating both private and public payer datasets. This analysis updated previous estimates and resulted in a substantially larger estimated economic burden than the first study by Birnbaum et al.[36] In the former study, excess medical costs amounted to approximately $2.5 billion. In this study, excess medical costs were estimated to be $23.7 billion. A small part of this discrepancy can be explained by the inclusion of caregiver burden in the most recent study, but excess caregiver costs accounted for only 8% of the total excess medical and drug costs. Excess medical and drug costs were included the Medicaid population in the most recent study, whereas in the previous study, this was not included. Medicaid patients and caregivers accounted for one-third of total excess medical and drug costs in the most recent analysis, contributing to the increased costs. Finally, per patient costs in the former study adjusted for demographics and a select number of pain-related comorbidities, but did not completely isolate the costs attributed to opioid abuse as total healthcare costs also reflected that of comorbidities that are not necessarily related to opioid abuse. In this study, comorbidities were measured using the Charlson Comorbidity Index, but the analysis did not adjusted for this. Controls had lower comorbidities compared to opioid abuse patients. Thus, these estimates may overstate the excess medical and drug costs per person that can be directly attributed to prescription opioid abuse.

Criminal justice costs in the most recent study were also larger compared to the previous study. This was explained by the inclusion of more criminal justice costs, such as lost properties

and correctional facilities. Costs related to lost workplace costs were also significantly higher in this study. In the previous study, workplace costs totaled at $4.5 billion, compared to $25.6 billion in this study. A large portion of this discrepancy is attributed to premature death. In both studies, DAWN data were used to capture prescription opioid-related deaths. However, opioid-related deaths have been shown to substantially increase during the time between the two studies. Furthermore, the data from DAWN used in the previous study did not at the time contain detailed demographic information by drug type, and an assumption was made that the number of deaths associated with drugs was proportional to the prevalence of nonmedical use of opioids obtained through NSDUH. Later editions of DAWN data contain this detailed information and can be used to provide a more accurate estimate of opioid-related deaths. Finally, presenteeism costs were also included in the final estimate of the recent study and were not accounted for in the previous study.

Several limitations exist with this analysis. Excess medical costs in this analysis may represent costs related to comorbidities or other healthcare utilization not directly related to opioid abuse. No adjustment was made to allow for differences in comorbidities between the two groups. To state that these excess medical and drug costs were attributable to opioid abuse implies causation, which is not established in this study. Like previous studies, this information can be useful to determine how much extra an average opioid abuser can cost, but does not measure the marginal cost of treating opioid abuse patients for abuse-related healthcare utilization. Thus, it can be less useful to inform interventions that address opioid abuse specifically. For example, interventions that may be aimed at reducing opioid abuse may not be directed towards reducing associated comorbidities. This may be the case among current abusers, where abuse interventions will not reduce pre-existing comorbid disorders such as

HIV/AIDS. Data are also lacking in this study on the types of resource utilization. Costs were neither stratified by the type of diagnosis, nor by drug type. It was not clear whether increased costs were due to poisoning events, acute substance abuse treatment and monitoring, or associated comorbidities.

**Hansen et al.[38] (2011)**

Hansen et al.[38] conducted a study evaluating the economic burden of the nonmedical use of opioids. The components he included were abuse treatment costs, medical complications, productivity losses, and criminal justice costs. All costs were apportioned to specific opioid analgesics. Substance abuse treatment costs included general hospital/inpatient costs, general hospital/outpatient costs, and costs incurred in substance abuse facilities and from physicians and other healthcare professionals. All costs were measured using a top-down approach. First, estimates were obtained from a report from the Substance Abuse and Mental Health Services Administration (SAMHSA) which evaluated national expenditures for substance abuse treatment. Subsequently pooled data from 2004 to 2006 were used to obtain the proportion of all opioid nonmedical use versus all drugs of misuse. Medical complications included the costs associated with HIV/AIDS, chronic hepatitis C, and neonatal care. Total HIV/AIDS and hepatitis C prevalence estimates were obtained and were apportioned to opioids based on the percent of HIV/AIDS cases attributable to intravenous drug abuse. These prevalence estimates were then multiplied by costs associated with HIV/AIDS or hepatitis C, respectively. Prevalence estimates for opioid withdrawal syndrome among newborns were obtained through the Healthcare Cost and Utilization Project Kids' Inpatient Database (HCUP KID). The cost of hospitalization was obtained using a fixed cost-to-charge ratio of 66%.

Criminal justice costs were based on costs of police services, the legal system, and incarceration based on data from the Bureau of Justice Statistics. These expenditures were stratified based on drug law violations. These costs were apportioned to specific opioids based on the percentages of all drug seizures. Costs to crime victims were also considered by using total costs of drug-related crime to victims.

Treatment costs for drug abuse were estimated at $11.5 billion in 2006 dollars. This was apportioned to prescription opioids for a total of $2.2 billion, or approximately 19%. In Birnbaum's first study, total treatment costs were apportioned to prescription opioid based on a ratio of treatment admissions for opioids to treatment admissions for all drugs of abuse and was not based on the ratio of reported opioid abuse to all drug abuse. In the second study, Birnbaum et al.[37] used a similar approach to Hansen et al. by apportioning the total treatment costs based on the ratio of reported opioid abuse to all drug abuse.

The authors apportioned total substance abuse costs to opioids based on the prevalence of all opioid nonmedical use to all misuse of drugs. This assumes that the intensity of healthcare services is constant across all drug misuse. For neonatal care, a fixed cost-to-charge ratio was used, and may not represent the true average cost since this varies according to hospital.

Although HIV/AIDS and hepatitis C are important considerations, these comorbidities can be a direct result of substance abuse only through contaminated paraphernalia used among injection drug users. Prescription opioid analgesics are largely available in oral formulations in tablet or capsule form. Although these formulations can be put into a liquid solution or suspension, many drug abusers can also use them orally. Furthermore, the methods employed by the authors make the inherent assumption that all cases of HIV/AIDS attributable to IV drug abuse are also attributable to prescription opioid analgesic drug abuse. This may be the case

with illicit opioids such as heroin, along with other non-opioid drugs of abuse such as cocaine or methamphetamine, but not with orally administered drugs. The extent to which these comorbidities can be attributed to prescription opioid abuse may be overstated.

*Gaps in the Literature*

One of the key components of previous analyses was that heroin was excluded. This was understandable since heroin is classified as a Schedule I drug and has no approved medical use in the United States. Since the intention of this analysis is to inform programs directed at the prevention and/or reversal of opioid poisoning in the United States, heroin poisoning will be an important component in this analysis since these programs are directed not only at injection drug users but also at prescription opioid abusers.

Another common feature of previous studies is that they all evaluate opioid abuse from a broad perspective. One study categorized healthcare utilization based on the location of service longitudinally, but did not provide specific reasons for utilization (i.e., poisoning, comorbidities, or other complications). With the exception of the study by McAdam-Marx et al.[39], these studies did not focus on evaluating costs of opioid poisoning, which is a narrower scope than what has been studied. Although McAdam-Marx evaluated the yearly costs after an opioid poisoning diagnosis, they did not calculate marginal costs associated with opioid poisoning nor did they provide indirect costs with opioid poisoning. Furthermore, the use of Medicaid data limited generalizability.

Another gap in the literature is that none have specifically attached these costs to specific opioids. Although the increases in opioid abuse have been seen in almost all common opioid types, the market share of each of these types differ. Additionally, opioids differ in their

pharmacological characteristics and mode of administration, which can render some opioids to be more likely to cause symptoms of opioid poisoning. It may be of interest when informing harm reduction programs to evaluate specific costs associated by opioid type as intervention efforts can focus on opioids most highly abused or most highly implicated in opioid poisoning.

Finally, sensitivity analyses were limited in the previous studies. Some sensitivity analyses were conducted primarily by changing the scenarios. However, each data input requires an assumption and error is introduced each time a variable is introduced from different datasets that sample from different populations. None of these studies employed a probabilistic sensitivity analysis, whereby variables are allowed to vary simultaneously based on predefined distributions.

## Section 2.2: Conceptual Frameworks

### Cost of Illness Studies

Opioid poisoning represents one component of costs associated with opioid misuse and abuse of opioids. It is an acute condition, and can be rapidly reversed upon expedient medical care. It is also important to note that opioid poisoning does not occur exclusively among those with a diagnosed substance use disorder, but can occur among medical users of the drug who use it for pain control.

An opioid poisoning event can be deconstructed into various events. At the highest level, we can consider all those in the "at-risk" population, which may include, but not limited to, those with prior substance use disorders and/or those who are prescribed opioid analgesics. Evaluating this requires a comprehensive dataset with the ability to track individual patients longitudinally

while evaluating prior histories. Once an individual has an opioid poisoning event, costs can be incurred through transport to the health system by ambulance, where the patient is evaluated in the ED. Depending upon the presentation of the patient (i.e., drugs involved, severity, comorbidities), the patient may be discharged or admitted into the inpatient setting, which is more costly than ED visits. Once admitted, patients can face various levels of resource utilization and lengths of stay, resulting in increased costs.

To quantify the costs associated with opioid poisoning, a cost of illness approach is used. This method for estimating the cost of illness was first detailed by Rice in 1966.[55] Rice provided a useful conceptual framework when evaluating the costs associated with an illness. This framework continues to serve as the basis for many cost-of-illness studies.[56] According to this framework, direct costs consist of those expenditures related to prevention, detection, treatment, rehabilitation, research, training, and capital investment in medical facilities. Although the evaluation of each component may not be possible given the limitations of available data, each should be addressed to identify limitations of the current research and areas for future research. These components are addressed below:

*Prevention*

In a recent report published by the CDC, there were 50 programs in 2010 that provided prescription naloxone to individuals who abuse opioids.[33] These programs vary in size and scope and include education and training for opioid abusers and caregivers along with the dispensation of prescription naloxone. Although these programs are important when evaluating the cost of opioid poisoning, no information is given with regards to the costs of maintaining such programs. Though information on costs is lacking, information on the number of vials dispensed by these programs is available.[33] Because naloxone is used for treatment rather than

poisoning, this is captured as a treatment cost. However, it is a total cost in programs that are designed to prevent opioid poisoning and related death.

*Detection*

Because of the nature of opioid poisoning, detection is less of a concern for costs. Unlike other diseases where medical expenditures are required to detect disease (i.e., diabetes, cancer, hypertension, etc.), opioid poisoning occurs suddenly and acutely. Costs may be incurred through the detection of opioid misuse and abuse, but are irrelevant when framed around opioid poisoning.

*Rehabilitation*

Rehabilitation is an important consideration for costs. Rehabilitation may include detoxification, which is primarily used for patients who develop dependence to opioids. This form of rehabilitation is more relevant when evaluating costs under the broader framework of misuse and abuse, but can also be relevant for opioid poisoning if patients are more likely to undergo detoxification after the poisoning event. Longitudinal data are necessary to evaluate subsequent healthcare utilization after the opioid poisoning event.

*Research*

Research related expenditures for misuse and abuse have been reported, but none have focused on research in opioid poisoning. Because research funding related to opioid poisoning can sometimes be captured under the umbrella of research related to opioid misuse and abuse, an exact number for funds dedicated solely for the purposes of opioid poisoning would be difficult to ascertain.

*Treatment*

Treatment costs include those incurred within the healthcare system (ED visits and inpatient stays), ambulance costs, and naloxone prescription costs. This evaluation directly measures ED costs and inpatient costs through the use of ED and inpatient databases. Naloxone prescription costs and ambulance costs are measured through the use of secondary datasets.

**Table 2.2: Components of Cost of Illness Studies**[55]

| | |
|---|---|
| Prevention | Naloxone prescription programs; A significant cost of these programs is captured by naloxone prescriptions, which are captured in treatment costs. Education is also an important part of these programs, but information on the costs to provide this education is lacking. |
| Detection | Detection is less important in acute events as the detection of the condition occurs at the moment of treatment. This is unlike chronic disease states where detection of disease occurs before treatment. |
| Rehabilitation | Most cases of opioid poisoning can be completely reversed if treated expediently. Rehabilitation may be required to address substance use disorders, but is outside the scope of this study. Data are lacking for rehabilitation costs for the fraction of patients who experience severe anoxia, which would be expected to result in brain damage. |
| Research | Costs associated with research in opioid misuse and abuse have been reported, but none of have reported on current research that is dedicated towards opioid poisoning. |
| Treatment | Treatment costs include those incurred in the hospital setting (emergency department and inpatient setting), ambulance transport, and naloxone prescription costs. |

Indirect costs are those that are imposed due to the loss of output to the economy. There are generally three sources of indirect costs: absenteeism, presenteeism, and premature death.

Absenteeism is measured by the number of absent days that are incurred as a result of the illness. Presenteeism refers to the reduction in productivity while working, and costs related to premature death are the lost future earnings of the decedent measure those. There are two general methods for estimating indirect costs: the human capital method, and the friction cost method. Debates in the literature have been documented regarding the validity of the human capital method compared to the frictional cost method.[57-59] The general principles of each and the motivations for their use are described here.

The human capital method was first proposed by Burton Weisbrod[60] in 1961 and followed by Rice and Cooper[55]. The human capital method ascribes value to an individual as a productive asset to society. Society refers to the entire population except for the individual being valued. It is based on the economic theory of marginal productivity of labor and makes several assumptions. These include full productivity and full employment in the market, competitive labor markets, negligible transaction costs and firms' behaviors to maximize profit.[58]

There are two ways to measure the value of life for an individual under the human capital method. The first considers the value of a person to others, which ascribes value based on the net contribution of the total output. The second, more common approach is to value the total output of an individual by measuring the individual's gross productivity.[60] The question of whether to use net productivity versus gross productivity has been a subject of debate. In both cases, the estimate is the value of potentially lost production or earnings instead of actual lost earnings. However, net productivity involves subtracting out consumption to be more consistent with the societal approach. Ultimately, gross productivity prevailed since no value to years of life would be attributed when consumption equals productivity.[58] To calculate lost productivity,

the net present value (NPV) of future earnings is calculated and defined by the following equation at age *a*:

$$NPV_a = \sum_{n=a}^{\infty}[Y_n P_a^n \frac{1}{(1+r)^{n-a}}]^{60},$$

where $Y_n$ = value of gross productivity of a person at age *n*; $P^n{}_a$ = the probability of a person at age *a* being alive at age *n*; and *r* = discount rate. The NPV can be calculated by age and sex, and should take into consideration labor force participation rates. The human-capital method traditionally does not account for unpaid labor, but can be incorporated into the valuation of human capital using the market-value approach or the opportunity-cost approach. The opportunity-cost approach values unpaid labor at the wage rate the individual would likely receive if in the work force, while the market-value approach uses the market price for the service.[58]

Critics of the human capital method claim that this method underestimates costs, as it does not value human life more than the economic productivity of the individual.[57] Others claim that costs are overestimated especially in the case of premature mortality since firms can hire someone who is unemployed, hire someone from another firm, or reallocate resources from within their own firms.[57] Critics also argue that absent time increases leisure time and adds to the overestimation of indirect costs, though this is complicated by the fact that the leisure time is spent while ill.[57] Finally, it is assumed that supply and demand conditions affecting potential incomes are the same throughout time as they were when these costs were estimated.[57] Despite some of these limitations, the human capital method is the most widely used method for valuing productivity costs.[61]

Another method used to evaluate indirect cost is the friction cost method.[62] The friction cost method assumes that if unemployment exceeds frictional unemployment, unemployed

individuals can replace sick persons after a "friction period". Firms must adapt during the friction period and can utilize existing labor reserves within the firm, postpone non-urgent work, or reallocate employees over the jobs until a new employee is hired. In this period, three possibilities can occur: production falls, remains equal at extra labor input and costs, or falls in spite of extra labor input and costs. Because of the lack of data on the exact magnitude of these losses and costs during the frictional period, labor costs of the absentee can serve as the best estimate of average indirect costs.[62]

Critics of the friction cost method cite that this method does not conform to neoclassical economic theory, which suggests economies are characterized by full employment and can adjust to disturbances without cost.[57] This is countered by proponents who suggest that neoclassical economic theory's assumptions are unrealistic given that unemployment is always existent.[57] Critics also question the ability of workers to make up lost work in short-term absences.[57] Nevertheless, the friction cost method and the human capital method are not expected to differ for short-term absences.[57] Valuation of the opportunity cost of labor beyond the friction period as zero is argued as not supported by neoclassical economic theory nor by empirical evidence.[57]

Although no consensus is given in the literature regarding which method for valuing productivity costs is superior, the human capital method remains the most widely and frequently used method for valuing these costs. Because of its broad use in the literature and its ease of implementation, the human capital method was employed in this analysis. This will also allow for easier comparisons to other studies, which have used the human capital method to measure productivity costs.

**Evaluation of Hospital Costs**

It is also of interest evaluate differences in costs, lengths of stay, and in-hospital mortality between patients hospitalized for opioid poisoning from three types of opioid analgesics: heroin, methadone, and non-methadone opioid analgesics. Each of these agents has distinct pharmacokinetic (PK) parameters that may result in varying degrees of poisoning severity. For example, heroin has a relatively short half life (about 8 minutes) with its metabolites having a half-life of approximately 22 minutes.[63] This is in contrast to methadone, which has a half-life of anywhere form 10 to 75 hours depending on a variety of factors.[64] Other opioid analgesics have half-lives that depend on the drug and the formulation, and can range from anywhere from 2 to 16 hours.[1] Hydrocodone and oxycodone, two of the most commonly prescribed opioid analgesics, have half lives of 2.5-4 hours and 3-5 hours, respectively.[1, 65] Pharmacodynamic (PD) properties also differ among opioid types. For example, the heroin-to-morphine ratio for analgesic potency is approximately 2:1[66], whereas commonly prescribed opioid analgesics oxycodone and hydrocodone have relative potencies of approximately 2:1 and 0.9:1, respectively.[67, 68] Other opioid analgesics have significantly higher relative potencies, such as fentanyl with a relative potency of about 80:1.[1]

Differences in the PK/PD characteristics in these agents may result in differences in the severity of opioid poisoning or the need for closer and extended monitoring. Given these differences, it is expected that methadone would confer the highest costs, length of stay, and in-hospital mortality compared to either heroin or other non-methadone opioid analgesics. The differences between heroin and non-methadone opioid analgesics may be less clear because the relative potencies and half -lives of hydrocodone and oxycodone do not differ substantially with heroin. This is also complicated by the fact that heroin is usually injected instead of being given

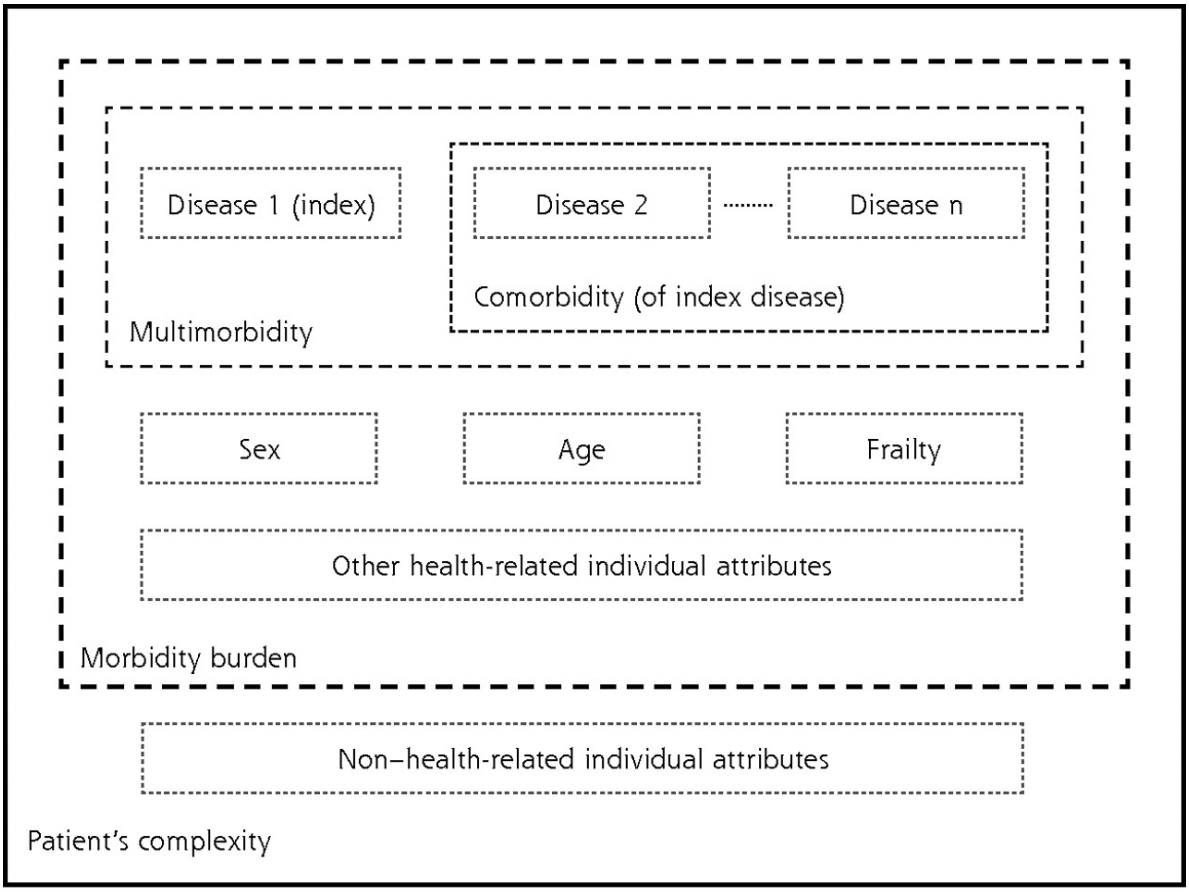
orally as with hydrocodone or oxycodone. However, because of the generally shorter half-life of heroin compared to opioid analgesics, it was hypothesized that heroin would result in lower costs.

The costs for hospitalization are complex and reflect both patient and hospital characteristics. Patient characteristics that may be involved with increased costs include demographic characteristics, the condition being treated, method of reimbursement, comorbidities, and the severity of illness of the patient. Hospital characteristics may include hospital bed size, location of the hospital, hospital ownership and teaching status. Each of these potential covariates is explained below. Because systematic differences may exist between patients of differing opioid types that are implicated in the poisoning event, conclusions regarding true differences in outcomes may be erroneous if these differences are not accounted for. These characteristics are discussed in further detail below.

*Comorbidities*

A comorbidity can be defined as "any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study."[69, 70] Thus, identification of comorbid disease requires an examination of conditions co-occuring with the index disease under study and the distinction of these conditions as either complications of the disease or true comorbidities. For example, if a patient is admitted for myocardial infarction and has congestive heart failure (CHF), CHF cannot be considered a comorbidity since CHF is an eventual complication of myocardial infarction. However, other conditions such as asthma or depression may be considered comorbidities. The greater the comorbidity burden, the greater the overall complexity of the patient (Figure 2.1).

**Figure 2.1 Framework for Disease Complexity**[69]




**Comorbidity:** presence of additional diseases in relation to an index disease in one individual.

**Multimorbidity:** presence of multiple diseases in one individual.

**Morbidity burden:** overall impact of the different diseases in an individual taking into account their severity.

**Patient's complexity:** overall impact of the different diseases in an individual taking into account their severity and other health-related attributes.

Those presenting with opioid poisoning may come from populations who have distinct comorbidity profiles. These comorbidities increase the complexity of the patient and can thus increase the cost of care for these patients in the hospital setting. Differences in the comorbidity profile between patients of differing implicated opioid types can confound the conclusions. It is

therefore important to adjust for these comorbidities to improve the ability to truly attribute differences in outcomes to the opioid types involved.

Several methods have been proposed to adjust for comorbidities. Two commonly used methods employed in database research are the Charlson Comorbidity Index and the Elixhauser method. A description of these methods is provided below.

The Charlson Comorbidity Index (CCI) is a weighted index that incorporates a selection of 19 diseases, each assigned a weight from 1 to 6 depending on the specific condition. Each of these scores is then summed to produce the final weighted index. The CCI was originally tested to predict 1-year mortality rates among women with breast cancer.[71] Adaptations to the CCI have been made to allow for linkage of the CCI to claims data via ICD-9-CM codes.[72, 73] Though the original CCI was validated in the breast cancer population for one-year mortality, the CCI has been validated in other applications as well.[74-77] Though nonetheless useful for adjusting for comorbidities, critics have called to attention limitations with the use of this index. One such criticism is that the weights applied to some conditions are outdated and have not been updated to reflect advances in medical treatment.[78] Such is the case with HIV/AIDS, which has the highest weight possible of "6" among the different conditions. Advances in the treatment and management of HIV/AIDS has significantly improved since the original weighting scheme was created in 1987. Though validated to predict 1-year mortality, the weights applied are somewhat arbitrary in their assignment, and the "true" weight for each of these condition may differ depending on the disease state and population under study.

Another way of adjusting for comorbidities is the Elixhauser method. The original Elixhauser method was specifically conceptualized as a way to adjust for comorbidities using

administrative inpatient datasets. The original measures included a list of 30 conditions that together were shown to be associated with increased length of stay, hospital charges and mortality in an inpatient setting.[79] In its original form, each of these conditions could be used in a regression model with 30 indicator variables that represent each of these 30 conditions to adjust main effects. Secondary diagnoses related to each of these 30 conditions were considered comorbidities only if they were unrelated to the diagnosis-related group (DRG) assignment at discharge. The latest iteration of the Elixhauser method in use by the Healthcare Cost and Utilization Project (HCUP) has been modified to include a total of 29 conditions after excluding cardiac arrhythmias due to concerns about reliability.[80] This method does not assume a specific weight for each of these conditions since each of these can be entered in a regression model separately as a regressor. Though advantageous in these regards, its use is limited when sample sizes are small as the degrees of freedom are taken up by the inclusion of all of the conditions in the regression model. Because Elixhauser method evaluates comorbidities in relation to specific DRGs, it is a more systematic method of evaluating comorbidities compared to the CCI. It has also been shown to perform better than the CCI in predicting survival.[81]

Both the CCI and Elixhauser method of adjusting for comorbidities are general comorbidity adjustment methods and do not incorporate other conditions which may be prevalent in specific subpopulations and which may be predictors of costs or other outcomes. Because patients with opioid poisoning may represent a unique subpopulation with other comorbidities that can increase costs, it is worth exploring other important comorbidities. A previous study by McAdam-Marx et al. reported a higher prevalence of particular comorbidities compared to a matched control in a Medicaid population.[39] The comorbidities of and their prevalence among abuse/dependence patients and controls are listed in Table 2.2. With the exception of alcoholic

hepatitis, motor vehicle and motor vehicle accidents, all other comorbidities shown in Table 2.3 were shown to be significant predictors of increased annual costs when considering prescription drugs, outpatient care, and inpatient care. These specific opioid abuse-related comorbidities identified by McAdam-Marx et al.[39] are discussed in further detail below.

**Table 2.3: Identified Comorbidities with Higher Prevalence in Opioid Abuse**

| | Abuse/dependence patients (%, n = 50,162) | Controls (%, n = 150,485) |
|---|---|---|
| Non-pain-related | | |
| Other substance abuse | 45.1 | 8.23 |
| Psychiatric disorders | 49.2 | 26.1 |
| HIV/AIDS | 14.5 | 3.1 |
| Endocarditis | 1.1 | 0.2 |
| Skin infections | 12.7 | 5.4 |
| Gastrointestinal bleed | 8.6 | 6.3 |
| Cirrhosis/chronic or acute liver disease | 7.3 | 1.7 |
| Hepatitis A,B, C | 17.1 | 2.4 |
| Alcoholic hepatitis | 0.4 | 0.1 |
| Other hepatitis | 1.4 | 0.2 |
| Pancreatitis | 1.7 | 0.6 |
| Sexually transmitted disease | 8.6 | 7.6 |
| Herpes simplex | 1.3 | 0.7 |
| Burns | 1.0 | 0.5 |
| Trauma | 31.2 | 19.8 |
| Motor vehicle accidents | 0.6 | 0.2 |
| Pain-related | | |
| Cancer | 3.4 | 1.2 |
| Back/neck | 27.9 | 1.5 |
| Arthritis | 27.3 | 1.4 |
| Neuropathic pain | 9.8 | 1.2 |
| Headache/migraine | 11.7 | 1.6 |
| Any pain | 50.0 | 1.3 |

Nonmedical opioid use is associated with a variety of comorbidities. Mental health disorders are particularly associated with nonmedical opioid use. Up to 70% of individuals with an opioid use disorder have a lifetime risk of having a mood or anxiety disorder, with major

depression being the most prevalent diagnosis.[82] It has been reported that up to 17% and 16% of nonmedical users of prescription opioids have depression and anxiety, respectively.[83] Nonmedical users of prescription opioids have a 1.2 to 4.3 and 1.2 to 3.0 times greater likelihood of having depression and anxiety compared non-users of opioids, respectively.[84] Conversely, patients with mood disorders (such as depression) or an anxiety disorder have been found to also have an increased likelihood of non-medical prescription opioid use.[84, 85] An association with these diagnoses and increased use of mental health services utilization have also been noted.[86] The correlation between mental health disorders and non-medical opioid use has even been shown to differ depending on the type of prescription opioid analgesic implicated, with non-medical Oxycontin users having a greater likelihood of having an anxiety disorder compared to other opioid analgesics.[84, 87]

Differences in the prevalence of mental health diagnoses have also been found to differ between opioid overdose decedents and other opioid users. In a Veterans Health Affairs (VHA) sample, a larger percent of opioid overdose decedents had a substance use disorder or psychiatric disorder when compared to non-decedent opioid users (39.5% vs. 9.8% and 66.4% vs. 33.6%, respectively).[88]

The prevalence of pain among non-medical prescription opioid users in various populations has been estimated to be between 14.5% and 61.5%.[84] As much as 61.5% of prescription opioid analgesic abusers had chronic pain and 81.8% have indicated that pain was the reason for initiating the use of these drugs.[84, 89] The presence of back pain and headache is a common occurrence in these users. A review of patients has demonstrated that 31% and 18% misusers of prescription opioid analgesics experienced back pain and headaches, respectively.[84, 90] More patients who were dependent on prescription opioids had any type of history of pain

(97.7% vs. 43.5%), acute pain before initiating opioid use (16.3% vs. 6.5%), chronic pain before starting methadone maintenance therapy (88.4% vs. 12.9%) than patients dependent on heroin only.[84, 91] Differences in pain-related diagnoses have also been noted among opioid overdose decedents. In a VHA sample, opioid overdose decedents had a higher prevalence of chronic bodily pains (78.4% vs. 69.3%), headache (12.0% vs. 6.6%) and injuries/acute pain (29.6% vs. 19.1%) when compared to all opioid users.[88]

Though the literature has focused on evaluating problematic opioid-taking behaviors in the non-cancer population, there have been none that focus on such behaviors among patients diagnosed with cancer-related pain. Patients with cancer-related pain represent a unique subset of patients with specific needs regarding their care, whether they are related to treatments directed at the cancer or the complications of the disease (i.e., pain, infections, etc.). Because cancer can greatly increase the complexity of care among these patients, it should be considered when controlling for costs, LOS and in-hospital mortality among opioid poisoning patients.

Sexually transmitted infections (STIs) are prevalent among illicit drug users. STIs such as HIV or Hepatitis C are not only transmitted by injection drug users through shared needles, but can also be transmitted via risky sexual encounters in this population along with other STIs. In one survey among illicit drug users in Columbus and Dayton, Ohio, between 22 to 26% exchanged drugs for sex within the past 30 days and 34% reported exchanging sex for money.[92] About 52% of respondents reported having had an STI during their lifetimes.[92] The high prevalence of STIs among illicit drug users merits consideration as a variable to control for when evaluating outcomes such as costs or LOS

Herpes simplex virus (HSV) is another specific STI that has been shown to be highly prevalent among illicit drug users. In a sample of non-injecting cocaine and heroin users in New York City, the seroprevalence of the HSV-2 strain of the virus was 60%.[93] Because of the high prevalence of this condition among heroin users and its inclusion as a factor for increased annual costs in previous literature,[39] it should be considered when evaluating hospitalization costs.

Substance use disorders are particularly prevalent among individuals with HIV/AIDS. Approximately 9% of all estimated new HIV infections were represented by injection drug users in 2009.[94, 95, 95] Individuals involved with injection drug use are at particular risk for blood-born pathogens due to practices relating to the sharing of needles with infected individuals. Since 2000, injection drug use has been implicated in approximately 28% of all new cases of AIDS.[96] Treatment of HIV and related complications is expensive. In 2005, it was estimated that HIV inpatient discharges cost approximately $13,290 on average.[97] Total yearly costs were estimated to be $19,912 in 2006.[98] Injection drug users with HIV have been shown to have greater incremental hospitalization costs than injection drug users without HIV ($1,752 per year in 2001).[99] Because HIV is a prevalent diagnosis among misusers and abusers of opioids and due to the high costs and morbidity associated with the disease, controlling for HIV/AIDS when evaluating inpatient costs, length of stay, and mortality in this population should be considered.

Any prior injection drug use has been identified as a risk factor for developing viral hepatitis.[100] The three most common forms of viral hepatitis are hepatitis A, B, and C. Hepatitis B and C are primarily transmitted through bodily fluids, such as the blood. Hepatitis A is usually transmitted through fecal-oral route.[101] The prevalence of hepatitis B among injection drug users has been estimated to be between 50.9%to 89.6% with an incidence of 0.9 to 4.8 cases per 1,000 injection drug users.[102-105] The prevalence of hepatitis C in this population has been estimated to

be between 60 to 90% in 2001.[105] The prevalence of hepatitis A is lower among injection drug users, but is still common. Cyclic outbreaks of hepatitis A in this population have been implicated in up to 30% of cases in different areas.[106-109]

Infective endocarditis is also associated with injection drug use. The number of hospitalizations for IDU-related endocarditis increased between 38% to 66% in the United States between 2001-2002 to 2002-2003.[110] Although mechanisms for infective endocarditis are unclear, reasons by which IDU results in IE include improper hygiene of the surrounding tissue, particulate matter in drug solutions, direct injection of bacterial loads, and drug-induced pulmonary hypertension with increased right-side turbulence.[111] Infective endocarditis can be life-threatening with high complication rates from deep infections, thromboembolic events, or severe sepsis.[112]

Cutaneous injection-related infections are skin infections (i.e., cellulitis, abscesses) that occur in up to 10% to 30% of all injection drug users.[113-115] These infections have been listed as being among the top reasons (along with pneumonia) for hospitalization among injection drug users.[99] Once hospitalized, life-threatening complications may result in deep infections into vital areas, necrotizing fasciitis, myositis, bacteremia, and sepsis.[116]

It is established that alcohol abuse is a co-occuring problem among opioid abusers. Approximately 12% to 14% of patients on chronic opioid therapy are reported to have concurrent alcohol use.[117, 118] Acute episodes of alcohol toxicity can induce alcoholic hepatitis especially among chronic users of alcohol.[119] Chronically excessive alcohol use has been linked with alcoholic steatohepatitis, or fatty liver disease, in up to 20% of alcoholics who undergo liver biopsies and severe cases are associated with a poor prognosis.[120, 121] Because alcohol

intoxication may occur concomitantly with opioid intoxication, it merits evaluating this as a risk factor for increased costs, LOS or inpatient mortality.

Other hepatitis may be considered especially for cases which involve concomitant acetaminophen toxicity. Branded and generic versions of Vicodin and Percocet contain acetaminophen in combination with hydrocodone and oxycodone, respectively. Because these products are combined, those that overdose on these agents are also at risk of acetaminophen toxicity in addition to opioid poisoning. A cardinal feature of acetaminophen toxicity is liver damage. Acute hepatitis may occur with acetaminophen and may complicate care and/or require further evaluation.

Though the mechanism of action is unclear and empirical evidence limited, opioid analgesics such as codeine and morphine have been suspected in acute pancreatitis.[122-125] In addition, acute pancreatitis may be precipitated by concomitant alcohol intoxication. Thirty percent of all cases of pancreatitis in the United States are attributable to alcohol consumption.[126]

*Demographics*

Other factors, can contribute to the overall complexity of a patient, such as age, sex, and other patient factors. These factors are discussed in further detail below.

*Age*

Because patient demographics are known to differ between opioid types and are associated with differences in costs, these characteristics have to be adjusted for in the model and explored as potential explanatory variables in increasing hospitalization costs in this population. Those that experience prescription opioid poisoning are more likely to be older than those who overdose on heroin. Patients of increased age are likely to have poorer health than younger

individuals. Additionally, differences in the physiology of older individuals may affect how disease is presented PK/PD effects of drugs may be altered in older individuals.[127, 128] It has been shown that older adults 2.8 to 8.7 times as likely to experience respiratory depression compared to younger adults, with those greater than 60 years of age having the greatest risks of respiratory depression.[129] The effect of age on health has translated to increased costs among opioid abusers, with those 65 years and older having up to 235% greater costs than those aged 12 to 18.[39]

*Sex*

Sex should also be explored as a potential confounder of increased hospitalization costs in this population if gender is associated with increased costs and independently associated with opioid type. For example, the mortality rate in 2008 for males was higher (5.9 vs. 3.7 per 100,000 population) despite having an equal rate of emergency department visits for the nonmedical use of opioid analgesics.[21, 130] It has been documented in the literature that females tend to have greater overall healthcare utilization and/or overall costs in a variety of settings.[39, 131, 132] If women seek more preventive care and services related to abuse and non-abuse related services, then they may be less likely to have severer presentations. Males may also be more likely to engage in riskier or more intense abuse-related behaviors that may result in worse presentations than females. If these hold true, then males may incur higher hospitalization costs than females. Conversely, an increase in the likelihood to seek medical care may result in greater and potentially more intense opioid use than men. Furthermore, women are more likely to report the presence of pain, higher severity, higher frequency, and longer duration of pain compared to men.[133] Another consideration is the physiological differences between males and females that could result in differences in opioid pharmacodynamics and pharmacokinetics. For

example, morphine is known to be more potent and have a slower onset and offset in women compared to men and women may require greater dosages of morphine to obtain the same therapeutic effect as males.[134] Females may also be more susceptible to opioid side effects such as nausea and vomiting compared to men.[129] In these cases, females may have higher hospitalization costs than males. Although the direction of the effect may be unclear, differences in medical utilization, psychosocial behaviors and physiology may play a role in differences in the costs for treating patients hospitalized with opioid poisoning.

*Race*

Race may also play a role in increased hospitalization costs. In fact, differences in race have been documented with blacks having increased costs compared to whites.[39] Some evidence suggests that whites may be more likely to experience side effects such as nausea and vomiting with the administration of opioid analgesics.[129] The direction of this effect has also been demonstrated when evaluating mortality. Among those with opioid users chronic pain and substance use disorders, whites were observed to have a greater risk of opioid overdose death compared to blacks.[88] Differences between white and African-American children have been observed, with the former exhibiting higher clearance of morphine due to genetic variations.[135] Race may also be used to explain socioeconomic status where other measures fail to capture the construct.[136]

*Socioeconomic Status*

Socioeconomic status can be thought of as a measure of three constructs: economic status, social status, and work status. These three constructs can be operationalized through income, education, and occupation, respectively.[137] Lower socioeconomic status has been linked to greater severity of disease at admission and/or longer length of stay in the inpatient setting,

although findings are mixed.[48-54] Furthermore, some evidence suggests that illicit prescription opioid users may have a higher socioeconomic status than heroin users.[138]

Patient-level socioeconomic variables are not always available in datasets. One way to control for socioeconomic characteristics in the absence of these variables is to use a proxy. Median household income is one such proxy that can be used in for socioeconomic status, with particular caveats.[139] Caution should be exercised when interpreting the effect of area-level income as a proxy for household income as there is large variability between these two measures.[140]

*Geographic Area*

Some evidence suggests that non-medical users of opioids and other drugs of abuse in rural location have poorer self-rated health, lower perceived importance of seeking medical treatment and may have greater psychological and alcohol use burden compared to those in an urban setting.[141] This may imply greater inpatient costs for these patients due to generally worse health.

*Payer Type*

Differences in the payer type may also result in differences in outcomes. Having Medicaid and being uninsured are associated with the highest adjusted costs and odds of in-patient mortality for major surgical operations.[142, 143] These differences may reflect differences in access to healthcare, generally poorer health, and differences in discharge practices.[142] This effect may depend on the types of conditions treated, however. For example, one retrospective study involving motor vehicle accidents found no effect.[144] Because of the potential differences in costs depending on payer type and because heroin users are likely to have different payer

types associated with them compared to prescription opioid users, it is important to account for these differences when assessing patient level hospital costs.

*Hospital characteristics*

Hospital costs can vary significantly by hospital and reflect a combination of inputs related to labor, capital, and supplies and have been shown to vary according to vary according to different characteristics.[145] Consideration of these characteristics is important when evaluating inpatient costs, as hospital level differences at each of these hospitals according to these characteristics may also influence cost. Each of these different components is discussed here.

Average costs per admission have been shown to be higher for urban hospitals compared to rural hospitals.[145, 146] For-profit hospitals have been shown to have higher average administrative cost per adjusted admission compared to not-for-profit and government hospitals.[145, 147] In a meta-analysis of hospital ownership, results were mixed, with wide variations with regards to the direction of the effect. Some studies showing lower costs associated with for-profit hospitals and some showing higher costs compared to non-profit hospitals, while differences between non-profit and government hospitals were not as notable.[148] Teaching facilities have been shown to have greater costs than non-teaching facilities, which may reflect the added costs of medical education within the institution.[146, 149] Finally, variations in costs according to hospital region (i.e., northeast, midwest, south, west) have been noted.[150]

Bed size can be important in predicting hospital costs per patients. In theory, larger hospitals should have lower costs per patient due to economies of scale.[151] However, empirical evidence supporting this theory is mixed, with some studies supporting this theory[152, 153] while

other studies have demonstrated diseconomies of scale.[154-156] Because of the potential for hospital size to influence hospital costs, hospital size should be adjusted for when evaluating hospital costs.

The importance of these hospital characteristics in calculating costs have led the Centers for Medicare and Medicaid Services (CMS) to adjust inpatient reimbursement accordingly. Inpatient reimbursement is based on an inpatient prospective payment system based on a Diagnosis Related Group (DRG) assigned for the particular inpatient admission, with each unique DRG associated with a specific reimbursement rate. CMS accordingly pays a higher reimbursement to higher wage areas, teaching hospitals, and hospitals that treat a large percentage of low-income patients (i.e., Medicaid and Medicare).[157]

Although these characteristics are discussed here with regards to cost, they can be extended to other processes or outcomes such as length of stay or mortality. Increases in cost can sometimes in large part be explained by increases in average length of stay and it has been shown the average length of stay is a significant driver of hospital costs.[156] The relationship between hospital costs and mortality is less clear. Although hospital mortality rate has been shown to have an inverse relationship with costs[156], other evidence has demonstrated parallel relationships with both mortality rates and costs.[158, 159] Due to the relationships between average costs, average length of stay, and hospital mortality rates, these hospital characteristics should be given consideration when evaluating each of these types of outcomes.

## Section 2.3: Summary

Prescription opioid misuse and abuse have been increasing in the past decade, and is associated with significant costs to society. Related opioid poisoning has also been increasing and has been responsible for an increasing number of deaths. Naloxone prescription programs have been implemented to reduce the incidence of opioid poisoning related mortality, but have primarily focused on injection drug use. Some efforts have broadened the focus to include prescription opioid abusers as well. Current literature does not provide the data necessary to quantify costs associated with opioid poisoning.

When evaluating costs associated with opioid poisoning, a cost-of-illness approach can be used. Costs should be as broad as possible given the data available, and may include a variety of costs associated with the treatment and prevention of disease. This approach can be used to quantify the direct and indirect (i.e., productivity) costs per year associated with opioid poisoning. The human capital method is the most frequently used method of ascribing value to lost human life, though alternatives exist. Quantifying the economic burden of opioid poisoning can inform efforts to intervene with opioid poisoning.

Variations in pharmacologic profiles exist with different opioids. In addition, different populations may use these agents. Opioids may differ in their propensity to cause hospitalization for opioid poisoning. They may also be different in terms of costs associated with the treatment opioid poisoning. When evaluating hospital costs, however, it is important to consider a variety of factors that may influence costs. These include patient characteristics such as age, sex, socioeconomic status, insurance status, race, comorbidities, among other characteristics. Hospital characteristics should also be considered as these are known to influence costs. An

examination of these costs can aid in determining which types of patient populations are most costly to treat with respect to opioid poisoning.

# Chapter III:

## Methods, Results and Discussion for Specific Aim I:

Quantifying the Economic Burden of Opioid Poisoning

### Section 3.1: Methods

*Databases*

This analysis used the 2009 Healthcare Utilization Project (HCUP) National Inpatient Sample (NIS) and the National Emergency Department Sample (NEDS) to produce national weighted direct medical costs and indirect costs for the treatment of opioid overdose in the United States for community hospitals. The HCUP databases are nationally representative datasets that are based on a 20% sample of hospitals that submit data to HCUP.

For indirect costs due to premature mortality, the 2009 Multiple Cause-of-Death file from the National Vital Statistics System (NVSS) was used to estimate mortality to obtain an estimate the lifetime costs of mortality secondary to opioid poisoning.

Weighted prevalence estimates for prescription opioid poisoning were estimated using 2009 Drug Abuse Warning Network (DAWN) data in the base case scenario. A more detailed description of the DAWN dataset is provided in Chapter V. Briefly, DAWN is a network of EDs from which cases of drug-related visits are identified. Cases in DAWN can be categorized into 8 types of cases, including suicide attempt, seeking detoxification, alcohol only (for ages < 21), adverse reaction, overmedication, malicious poisoning, accidental ingestion, and other [160]. In this analysis, opioid poisoning cases are defined to be cases classified in DAWN as suicide attempt, overmedication, malicious poisoning, or a category labeled “other”. To limit cases that may be

likely to present with reasons other than for poisoning (i.e., withdrawal, need for detoxification, psychiatric diagnoses), those who were referred to detoxification, admitted to a chemical dependency/detoxification setting, or psychiatric unit were excluded. The category representing adverse reactions was excluded since these patients may present with other symptoms that are not necessarily related to opioid poisoning. Because it is unknown what percent of "adverse reactions" is likely to constitute opioid poisoning, these cases were excluded in the base case analysis. Cases classified as "adverse reactions" were subsequently included in sensitivity analyses. The DAWN dataset was also used to estimate the prevalence of specific opioids to estimate opioid-specific costs.

*Direct Costs Estimation*

A bottom up approach was used to estimate total direct treatment costs associated with opioid poisoning. To use this approach, the estimated mean treatment costs were estimated using the NEDS and NIS databases. Ambulance transport and prescription naloxone costs were later added to the total amount to arrive at an estimate of total direct costs. All cases of opioid poisoning were identified using ICD-9-CM codes. These codes and their accompanying descriptions are described in Table 3.1 below:

**Table 3.1: Opioid Poisoning ICD-9-CM Codes**

| | Description |
|---|---|
| E850.0 | Accidental poisoning by heroin |
| E850.1 | Accidental poisoning by methadone |
| E850.2 | Accidental poisoning by other opiates and related narcotics |
| 965.0 | Poisoning by opium (alkaloids), unspecified |
| 965.01 | Poisoning by heroin |
| 965.02 | Poisoning by methadone |
| 965.09 | Poisoning by other opiates |

Costs for emergency department (ED) visits that did not result in hospitalization ("treat-and-release" or T&R) were identified in the NEDS database. T&R visits include ED visits in which the patient died in the ED, was admitted to a different hospital or was treated and subsequently discharged. These dispositions were defined in NEDS according to the "ed_event" variable, which defines the disposition according to the following classifications: (1) ED visit in which the patient is treated and released, (2) ED visit in which the patient is admitted to this same hospital, (3) ED visit in which the patient is transferred to another short-term hospital, (9) ED visit in which the patient died in the ED, (98) ED visits in which patient was not admitted, destination unknown, (99) ED visit in which patient was discharged alive, destination unknown (but not admitted). In this analysis, categories (1), (3), (9), (98) and (99) were considered as "treat-and-release" visits for the purposes of estimating ED costs.

Although the NEDS database contains total charges, no standard mechanism is in place to convert these charges into costs. A preliminary analysis conducted by HCUP provided cost to charge ratios based on hospital characteristics (Appendix B, Table B.1).[161] Though not useful for determining an individual hospital's cost-to-charge ratio (CCR), these estimates are nonetheless useful in estimating an average cost. The procedure used to estimate these CCRs is further explained in Appendix B.

Physician fees in the ED were estimated upon the basis of physician fee codes contained in the NEDS databases. The database captures up to 15 Current Procedural Terminology (CPT) codes that were used to bill for physician services. Each CPT code was linked to Centers for Medicare and Medicaid Services (CMS) national payment amounts publically available from the CMS.[162] Once the payment amount was linked to the CPT code, the sum for all CPT codes for each of these visits was calculated.

Cases of opioid poisoning in the inpatient setting were identified using the NIS dataset using the same ICD-9-CM diagnoses used in Table 3.1. Charges were converted to costs using hospital-specific CCRs provided by HCUP. The CCR file contained all-payer inpatient CCRs and the group average all-payer inpatient CCRs. Because not all hospitals have hospital-specific CCRs, the group average all-payer inpatient CCR was used where hospital-specific CCRs were missing. Eighty-nine percent of hospitals in the dataset had hospital specific CCRs.

Ambulance costs were obtained from a Government Accountability Office report in 2006. [163] The proportion of ambulance utilization for all ED visits was assumed to be 38% and was based on an estimate that provided ambulance utilization information on various mental health ED visits. [164] Drug costs were based on the average wholesale price (AWP) obtained through the 2012 *Red Book*. [165] The total number of prescription naloxone vials dispensed per year was obtained from a 2012 report produced by the Centers for Disease Control and Prevention (CDC). [33] Direct costs were adjusted to 2011 U.S. dollars using the medical component of the CPI. [166]

*Multiple Imputation Procedures for Direct Costs*

Charges were missing in approximately 20% of the ED visits and CPT codes were missing for 26% of the visits. Charges were missing in approximately 3.7% of included inpatient visits. Therefore, multiple imputation procedures (Markov Chain Monte Carlo method) were performed to estimate these values. [167] To implement this procedure, 5 separate imputations were created according to the relationship with these values to other variables in the dataset. The relative efficiency[168] of using *m* imputations for a proportion of missing data (γ) is given by:

$$RE = (1 + \frac{\gamma}{m})^{-1}$$

This resulted in a relative efficiency of 96% and 95% for the ED charges and physician fees. The relative efficiency for the estimation of charges in the inpatient dataset was 99%. Variables in the multiple imputation procedure for ED visits included number of CPT codes, number of diagnoses, number of procedures, age, sex, intent of self-harm, payer status, urban/rural status of hospital, hospital ownership, region, teaching status, and opioid type. In addition, the total physician fees were added as a variable for imputed ED charges and vice versa. For the inpatient imputation procedure, number of procedures, length of stay, age, sex, sex, payer status, urban/rural designation, teaching status, race, hospital bed size, government ownership, hospital region, APR-DRG severity index, average wage index and Elixhauser comorbidities were used to impute missing charges. Each imputation incorporated random variation, accounting for uncertainty in the imputed values. Once these 5 imputations were created, results were combined incorporating the between- and within-imputation variance. SAS © version 9.3 (SAS Institute Inc., Cary, NC) was used to conduct the multiple imputation procedures.

*Indirect Costs Estimation*

Indirect costs were calculated from lost productivity due to mortality, absenteeism, and foregone household activities. Indirect costs were calculated by using data obtained from an analysis from Grosse et al.[169] In the analysis, the daily production value (DPV) was calculated based on the average daily hours working at a job, hours of household service, and hourly compensation for each by sex and age group. The DPV was inflated to 2011 U.S. dollars using the Bureau of Labor Statistics' Employment Cost Index (ECI) for all civilian workers.[170] The DPV was then multiplied by the average length of stay for opioid analgesics in the inpatient

setting. Three days of recovery time for ED visits and 7 days for inpatient stays post-discharge was assumed. This was based on recommendations on convalescence times for poisoning.[171]

Mortality was estimated from the 2009 Multiple Cause of Death file from the NVSS. This system records approximately 99% of all registered deaths in the United States. For patients that die of non-natural causes, such as in cases of poisoning, it is required that coroners and medical examiners single out the cause of death. Included in the file is the underlying cause of death identified by International Classification of Diseases 10 (ICD-10) codes, record axis fields, and place of death. The record axis fields contain additional ICD-10 codes that allow for further characterization of the manner of death and may also include comorbidities that were involved in the causal pathway of the death. Decedents of opioid poisoning were identified using this process: 1) Decedents due to poisoning due to narcotics and psychodysleptics and unspecified drugs were identified, (ICD-10 code X42, X44, X62, X64, Y12, and Y14). 2) Among those identified in (1), those where opioids were the contributory cause in the record axis fields (T40.0-T40.3) were selected. It should be noted that 'X64' (i.e., unspecified drugs) was included to capture all relevant poisoning cases. Combining the X- and Y-codes with the T-codes for opioids in the record axis fields helps to ensure that opioids were a contributory cause of the poisoning. Descriptions of each ICD-10 code are provided below in Table 3.2. The mortality file was analyzed using SAS © version 9.3 (SAS Institute Inc., Cary, NC).

Once mortality estimates were calculated, mortality costs were estimated by linking lifetime productivity estimates by age and sex provided by Grosse et al., incorporating household and market productivity.[169] These costs were adjusted to 2011 dollars using the ECI for the wages and salaries for all civilian workers.[170] A discount rate of 3% per annum was assumed.

**Table 3.2: Opioid Poisoning ICD-10 Codes**

| | Description |
|---|---|
| X42 | Accidental poisoning by and exposure to narcotics and psychodysleptics [hallucinogens], not elsewhere classified |
| X44 | Accidental poisoning by and exposure to other and unspecified drugs, medicaments and biological substances |
| X62 | Intentional self-poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified |
| X64 | Intentional self-poisoning by and exposure to other and unspecified drugs, medicaments and biological substances |
| Y12 | Poisoning by and exposure to narcotics and psychodysleptics [hallucinogens], not elsewhere classified, undetermined intent |
| Y14 | Poisoning by and exposure to other and unspecified drugs, medicaments and biological substances, undetermined intent |
| T40.0 | Opium |
| T40.1 | Heroin |
| T40.2 | Other opioids |
| T40.3 | Methadone |

Because abusers of these medications are likely to have lower workplace productivity and/or reduced labor participation, it is necessary to adjust productivity costs to reflect this. Illicit drug use has been estimated to result in a reduced productivity of between 17 and 18%.[172] Illicit drug use was defined as use of Schedule I drugs (i.e., heroin, marijuana, etc.) and non-medical use of licit drugs (i.e., opiates). This estimate was used to adjust lost productivity downwards.

The base case scenario did not include reduced productivity due to cancer. This was tested, however, in the sensitivity analysis. The prevalence of cancer is likely to be higher among opioid users, meriting further consideration of workplace productivity in this population.

Based on the percent of opioid poisoning decedents with cancer reported by the study by Bohnert et al.[88], it was assumed that 8 percent have an accompanying cancer diagnosis. Kroenke et al. performed a study evaluating patients with cancer-related and/or depression and estimated that 43% of participants were unable to work due to health related reasons.[174] Multiplying 8% by 43% yields a value of approximately 3%. Assuming that cancer patients have no productivity whatsoever, the upper limit for the decrement in total productivity losses is assumed to be 8%.

*Calculation of Costs per Event*

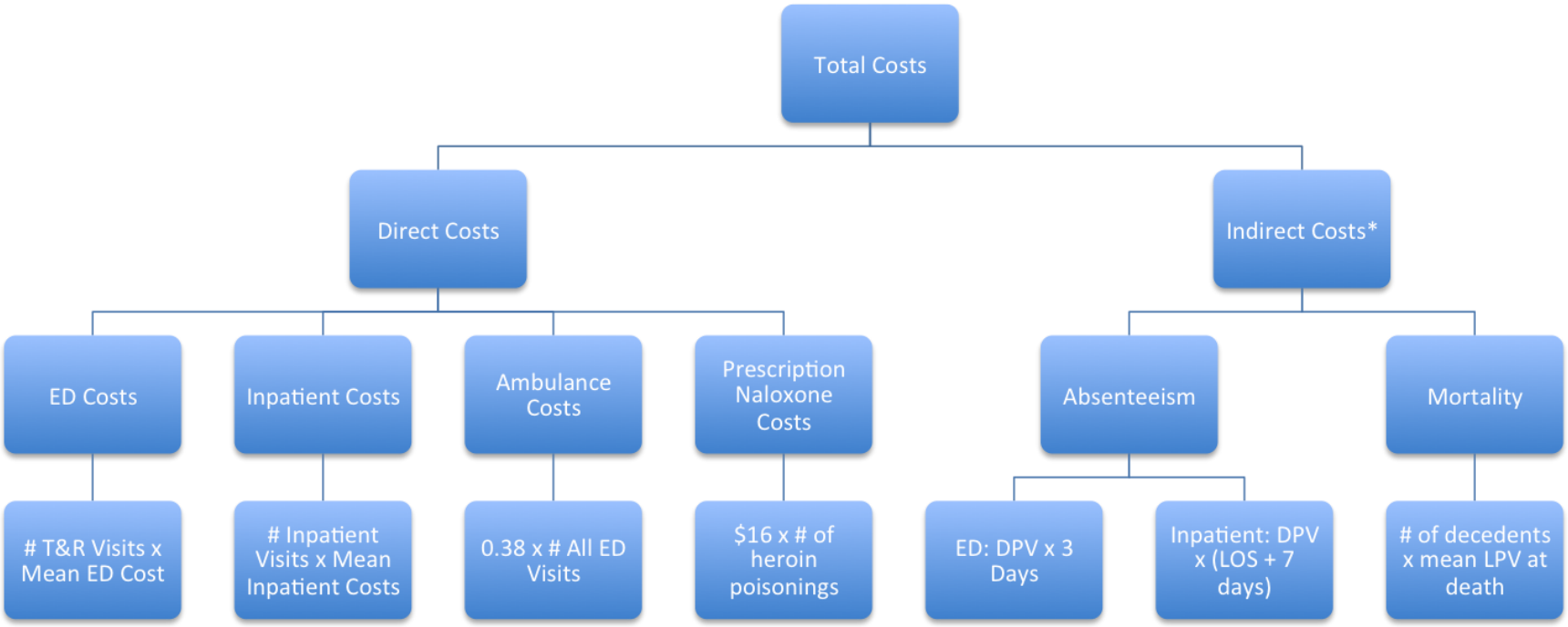
When calculating the cost per poisoning event, it was assumed that all poisoning cases resulted in a healthcare encounter or death. This assumption had to be made since the data available does not contain information on opioid poisoning cases that do not result in a healthcare encounter. Additionally, no studies have reported the prevalence of poisoning cases not resulting in an encounter due to difficulties in detecting and measuring these cases. Preventive prescription naloxone costs were not considered in calculating the direct costs per event. Details for calculating the costs per event are provided in Appendix A.

*Calculation of Opioid-Specific Costs*

Opioid-specific direct costs and absenteeism costs were estimated by multiplying the prevalence of each opioid by the mean costs. Mean costs for heroin were multiplied by the prevalence for heroin, while mean costs for prescription opioids were multiplied by the prevalence of each of the prescription opioids. An exception was made for methadone, where methadone-specific costs obtained in HCUP ($2,144 in the ED and $10,683 in the inpatient setting) were multiplied by the prevalence estimates for methadone. Opioid specific costs were calculated separately for ED and inpatient visits. For costs related to mortality, mean methadone mortality costs were multiplied by the prevalence of these two opioids in the NVSS dataset.

Mean non-methadone, non-heroin opioid costs were then multiplied by the prevalence of non-methadone, non-heroin mortality estimates to obtain a total estimate within this category. Then, the proportion of specific opioids from non-heroin, non-methadone opioid-related ED visits was calculated in the DAWN dataset. A top-down approach was then used to apportion the total costs based on the proportions obtained from the DAWN data.

**Figure 3.1: Costs Flowchart**




T&R = treat-and-release; ED = emergency department; DPV = daily production value; LPV = lifetime production value

*Indirect costs were reduced down by 17.5% in base case scenario to account for the reduced productivity among substance abusers.

*Sensitivity Analysis*

For the base case scenario, a one-way sensitivity analysis was performed on each of the following parameters: inpatient costs, ED costs, ambulance run costs, lifetime production values for men and women (for mortality), percent of decedents with cancer, daily production values for men and women (for absenteeism), proportion of ED visits involving an ambulance run and cost per ambulance run, and inpatient recovery time. Mean inpatient and ED costs or expenditures were varied using the lower 5$^{th}$ and higher 95$^{th}$ percentiles. Lifetime and daily production values and the reduction in DPV were varied between a 10% and 25%. The proportion of ED visits involving an ambulance run was varied between +/- 25% of the base estimate. Ambulance costs were varied within the 95% confidence interval reported in the GAO report.[163] Inpatient recovery time was varied between from 0 days to 14 days and ED recovery time varied between 0 and 7 days. A tornado diagram was created to demonstrate the greatest sensitivity to costs with respect to each of the variables tested.

Another set of sensitivity analyses was performed on the prevalence of ED T&R visits estimated from the DAWN dataset. The base case scenario excluded referrals or admissions to detoxification, withdrawal treatment, or psychiatry, and excluded cases classified as adverse reactions. Other scenarios were tested in the sensitivity analysis using a combination of the restricted disposition types and inclusion/exclusion of adverse reactions. The prevalence as estimated using ICD-9-CM codes in HCUP NEDS and NIS were also used to provide an estimate of opioid poisoning.

To simultaneously account for uncertainty in the inputs, a probabilistic sensitivity analysis was performed for costs per poisoning event and total costs, stratified by opioid poisoning type (heroin vs. prescription opioid vs. all). A total 10,000 simulations were

performed for each category of costs. All inputs used to estimate costs were varied simultaneously according to a pre-specified distribution. Gamma distributions were used for costs and were parameterized based on the means and standard errors. Prevalence estimates and drug costs were varied randomly +/- 50% of the estimated values using uniform distributions. A beta distribution was fit for the proportion of ED visits that involved an ambulance. Finally, the reduction in productivity due to reduced labor participation for substance abusers was varied randomly between 10% to 25% using a uniform distribution. Once all simulations were performed, non-parametric 95% confidence intervals were constructed using the lower and upper 2.5% of the range of values. Probabilistic sensitivity analyses were conducted using Microsoft Excel 2011.

## Section 3.2: Results

Using DAWN estimates, the prevalence of opioid poisoning visits to the ED was estimated to be 534,490 in 2009, or 174 per 100,000 population. Approximately 75% of all opioid poisoning visits involved prescription opioids only, while the rest involved heroin and combinations. Approximately 33% resulted in an inpatient admission. Table 3.3 provides prevalence estimates of specific prescription opioids by patient disposition (treat-and-release vs. hospitalized). A total of 16,205 opioid poisoning mortalities were found in the dataset, of which 3,282 involved heroin and 12,923 involved prescription opioid analgesics.

**Table 3.3: Prevalence Estimates for Opioids in the ED and Inpatient Setting**

| | Weighted n (unweighted n) | Sources |
|---|---|---|
| **Treat and Release** | | |
| Heroin | 109,269 (14,280) | |
| Prescription Opioid | 293,184 (19,948) | |
| Oxycodone | 108,576 (5,765) | |
| Hydrocodone | 66,149 (4,467) | |
| Unspecified | 57,420 (4,317) | |
| Methadone | 44,005 (4,681) | |
| Morphine | 21,138 (1,297) | 2009 DAWN Data |
| Fentanyl | 14,793 (671) | |
| Hydromorphone | 10,531 (731) | |
| Propoxyphene | 6,936 (298) | |
| Codeine | 7,604 (599) | |
| Other | 2,860 (123) | |
| All | 402,453 (34228) | |
| **Inpatient Admissions** | | |
| Heroin | 23,941 (4,298) | |
| Prescription Opioid | 108,106 (7792) | |
| Oxycodone | 36,574 (2117) | |
| Hydrocodone | 27,602 (1811) | |
| Unspecified | 21,779 (1771) | |
| Methadone | 16,286 (1535) | |
| Morphine | 9,542 (729) | 2009 DAWN Data |
| Fentanyl | 4,744 (351) | |
| Hydromorphone | 3,628 (313) | |
| Propoxyphene | 3,771 (208) | |
| Codeine | 3,401 (278) | |
| Other | 793 (42) | |
| All | 132,047 (12090) | |
| **Mortality** | | |
| Heroin | 3,282 | 2009 NVSS Multiple Cause of Death File |
| Prescription Opioid | 12,923 | |
| All | 16,205 | |
| **Other** | | |
| Percent ambulance usage | 38.2 | Larkin et al. [164] |
| Yearly prescription naloxone vials | 38,860 | MMWR Report [33] |

Table 3.3 displays prevalence estimates for treat-and-release (T&R) ED visits, inpatient admissions, mortality, ambulance utilization, and yearly prescription naloxone vials dispensed at naloxone prescription programs. Prevalence of mortality for specific prescription opioids not shown since drug-specific mortality information is unavailable.

*Direct Costs*

The average direct cost per poisoning event was estimated to be $4,006. The average direct costs per poisoning event were lower for heroin than for prescription opioids ($3,198 vs. $4,255). The mean ED treatment cost for all opioids was estimated to be $1,832 for all opioids, with prescription opioid treatment costs with prescription opioids having higher costs being higher compared to heroin ($1,967 vs. $1,379). The total estimated direct costs to the United States were estimated to be approximately $2.2 billion per year. Prescription opioid poisoning accounted for 80% of all direct medical costs. Total direct costs for each component after applying prevalence estimates are provided in Table 3.4. Figure 3.2 provides estimates of cost by specific prescription opioid. Total direct costs by prescription opioid were highest for oxycodone ($616 million), hydrocodone ($428 million), unspecified opioids ($350 million), and methadone ($289 million).

*Indirect Costs*

The estimated indirect cost per opioid poisoning event was $33,267. This was higher for prescription opioids ($34,285) than for heroin ($30,594). When evaluating absenteeism costs only, prescription opioids were estimated to have greater costs than heroin, ($621 vs. $584). Total indirect costs to society were estimated to be $18.2 billion.

The average length of stay in the inpatient setting was estimated in NIS at approximately 4 days among all opioid types. Assuming 2 days for recovery time after ED discharges and 7 days recovery time for inpatient discharges, the total absent time was assumed to be 3 and 11 days, respectively [171]. After multiplying by the respective prevalence estimates, the total absenteeism costs of heroin and prescription opioids were $79 million and $256 million, respectively. Total absenteeism costs for all poisonings were estimated to be $335 million.

Total mortality costs were estimated at $17.9 billion per year. Mortality costs attributed to heroin accounted for approximately $4.1 billion, and prescription opioids accounted for $13.9 billion. The greatest mortality costs were attributed to methadone ($5.1 billion), followed by oxycodone ($3.3 billion) and hydrocodone ($2.2 billion). Indirect costs per event and total indirect costs for each of the general opioid types (heroin vs. prescription opioid) are listed in Table 3.5. Total apportioned mortality costs for each of the specific prescription opioid types are shown in Figure 3.3.

*Total Costs*

Combining all cost components yields a total yearly cost of approximately $20.4 billion per year. Mortality costs were the largest component of costs, representing approximately 87% of the total costs associated with opioid poisoning. The total cost for prescription opioids and heroin was $15.9 billion and $4.6 billion, respectively. The average cost per opioid poisoning event when considering all sources of costs was $37,274. The cost per case for prescription opioids was greater than for heroin ($38,541 vs. $33,793).

**Table 3.4: Direct Costs in Opioid Poisoning**

| Direct Costs | Mean Cost (SE) | Total Costs | Sources |
|---|---|---|---|
| **Inpatient Costs** | | | |
| Heroin | $9,988 (410.54) | $239,122,708 | 2009 HCUP NIS, 2009 |
| Prescription Opioid | $9,696 (126.58) | $1,048,169,879 | HCUP Cost-to-charge |
| All | $9,723 (122.66) | $1,287,204,213 | ratio files |
| **ED T&R Costs** | | | |
| Heroin | $1,379 (28.07) | $150,681,951 | 2009 HCUP NEDS, |
| Prescription Opioid | $1,967 (22.16) | $576,789,271 | HCUP ED Costs Report |
| All | $1,832 (16.37) | $727,493,595 | [161] |
| **Physician ED Costs** | | | |
| Heroin | $173 (4.37) | $18,903,537 | 2009 HCUP NEDS, 2009 |
| Prescription Opioid | $182 (2.25) | $53,486,715 | CMS National Payment |
| All | $181 (1.99) | $72,443,289 | Amounts [162] |
| **Ambulance Costs** | | | |
| All | $504 (21.38) | $26,293,934 | 2006 GAO Report [163] |
| **Prescription Naloxone*** | | | |
| All | $16 | $633,818 | 2012 Red Book [165] , BuyEMP [175] |
| **Direct Cost per Event** | | | |
| Heroin | $3,199 | $435,061,497 | |
| Prescription Opioid | $4,255 | $1,755,699,294 | |
| All | $4,006 | $2,197,529,605 | |

The estimated mean costs, standard errors (where appropriate), total costs, and data sources are displayed. Total costs for inpatient costs, ED costs, and physician ED costs are obtained by multiplying prevalence estimates by their respective mean costs. Total costs for ambulance transport and care is calculated using the total prevalence estimates and the percent of ambulance use reported by Larkin, et al. [164] Cost per opioid poisoning event reflects the proportions of poisoning cases defined as "Treat-and-Release" (T&R), inpatient cases, and deaths. Total combined direct costs are the sum of all direct costs (See Appendix A)

*Prescription naloxone attributed towards costs for heroin-related poisoning only.

**Table 3.5: Indirect Costs in Opioid Poisoning**

| | Cost per Event ($)* | Total Cost ($, thousands)** |
|---|---|---|
| **Absenteeism Costs** | | |
| Heroin | 584 | 79,307 |
| Prescription Opioid | 621 | 256,173 |
| All | 610 | 334,648 |
| **Mortality Costs** | | |
| Heroin | 30,010 | 4,075,566 |
| Prescription Opioid | 33,664 | 13,887,512 |
| All | 32,657 | 17,907,232 |
| **All Productivity Costs** | | |
| Heroin | 30,594 | 4,155,966 |
| Prescription Opioid | 34,285 | 14,143,685 |
| All | 33,267 | 18,241,881 |

*The cost per event for all productivity costs are weighted based on the proportions of identified poisoning cases that result in treat-and-release ED visits, inpatient admissions, or mortality.

**Total estimated costs are based on the product of the cost per event multiplied by the total prevalence of opioid poisoning. Productivity costs were obtained from Grosse, et al. [169] and prevalence estimates (Table 2)

Direct and absenteeism costs by opioid are depicted in Figure 3.2. Oxycodone, hydrocodone, and unspecified opioids (i.e., opioids NOS) and methadone were associated with the highest direct and absenteeism costs combined ($718 million, $499 million, $408 million, and $332 million, respectively). Mortality estimates by opioid are depicted in Figure 3.3. Methadone, oxycodone, and hydrocodone were estimated to have the highest total mortality costs ($6.4 billion, $5.5 billion, and $3.6 billion, respectively).

**Figure 3.2: Direct and Absenteeism Costs by Opioid**

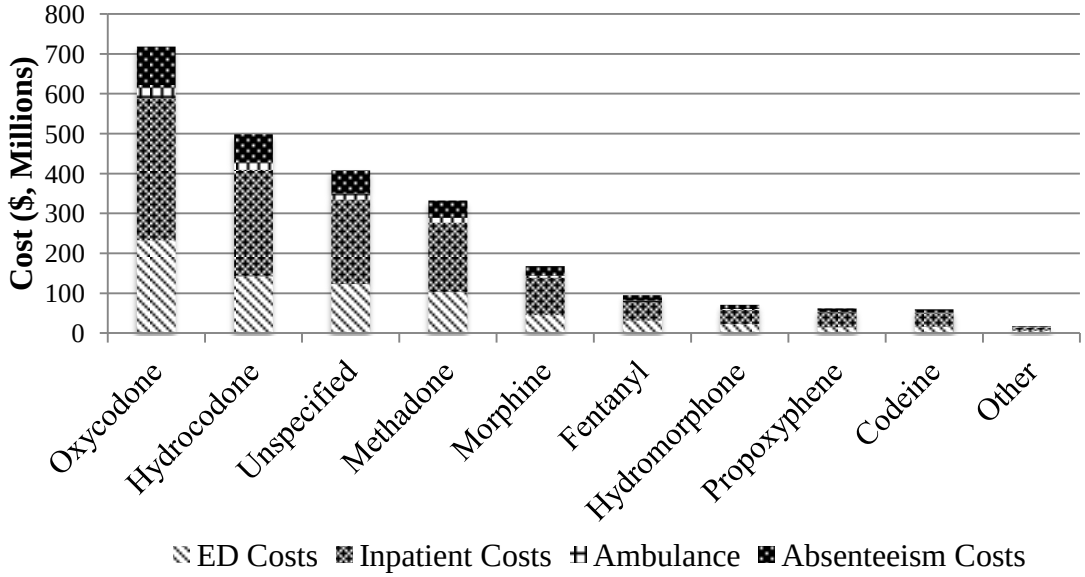
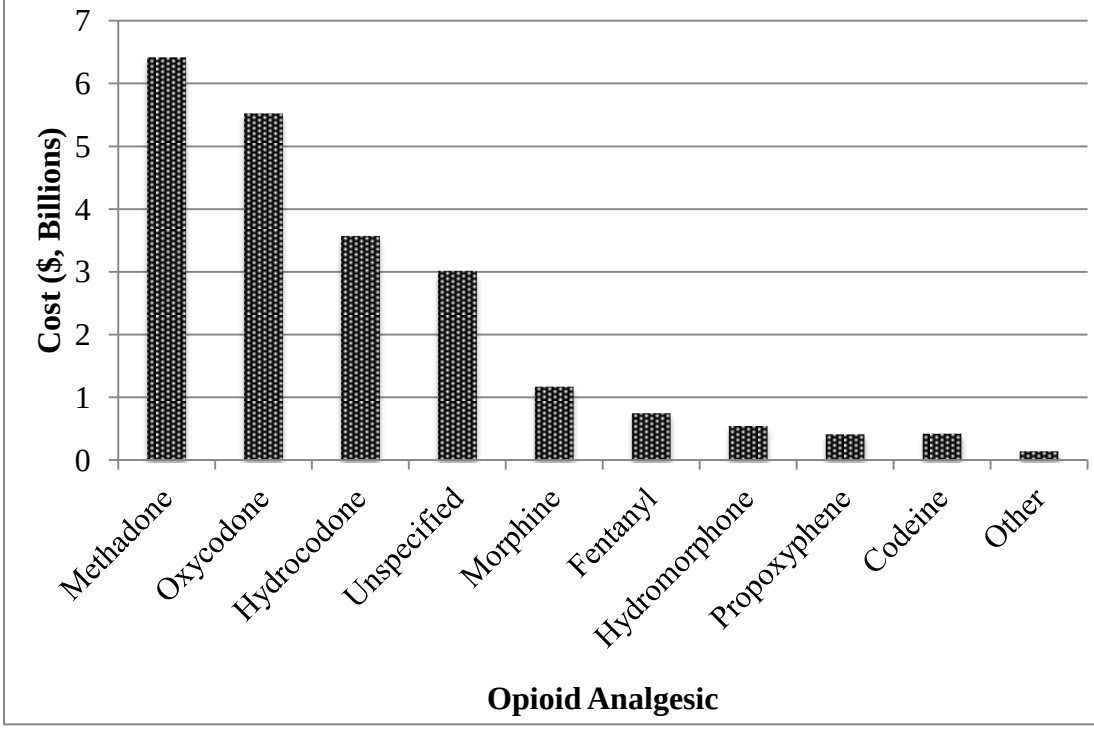



**Figure 3.3: Mortality Costs by Opioid**



*Sensitivity Analysis*

One-way sensitivity analyses on select variables are depicted in the tornado diagram in Figure 3.4. Costs were most sensitive to the discounting scenarios. Assuming a discounting scenario of 10% yielded an estimate of $10.6 billion, while assuming a 5% discounting scenario yielded an estimate of $16 billion. Varying the DPV between 10% and 25% yielded estimates between $22.1 and $18.8, respectively. Total cost estimates between the most conservative prevalence estimates (HCUP) and liberal DAWN estimates (all relevant DAWN cases) varied between $18.8 billion and $21.7 billion. When analyzing direct costs only, costs ranged from $816 million in the most conservative case to $3.3 billion in the most liberal case. Specific estimates resulting from the different combinations of "restricted dispositions" and "excluded adverse reactions" are provided in Table 3.6. Minimal differences in total overall costs were observed for other variables.

In the base case analysis, opioids classified as "opioid, not otherwise specified (NOS)" were considered to be prescription opioids. When this category was instead considered as heroin poisoning patients, the total estimate for heroin poisoning was estimated to be $5.0 billion (compared to $4.6 billion in the base case) with a cost per poisoning event of $22,556 (compared to $33,793 in the base case). Prescription opioids were estimated to have a total cost of approximately $15.5 billion (compared o $15.9 billion in the base case) with a cost per poisoning event of $47,307 (compared to $38,541 in the base case). Total estimates were maintained at $20.4 billion.

**Figure 3.4: One Way Sensitivity Analysis on Selected Variables**

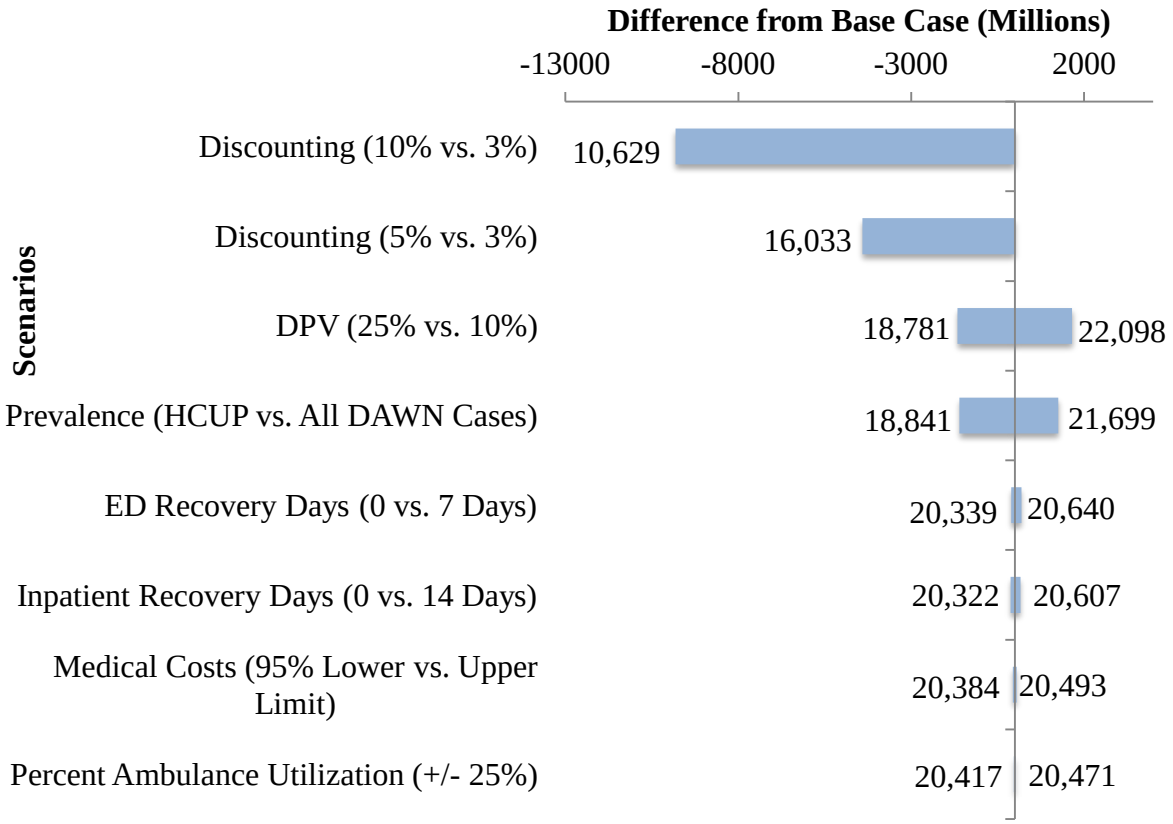



**Table 3.6: Sensitivity Analysis on Prevalence of ED Visits and Inpatient Stays**

| Scenarios | Restricted Disposition | Excludes Adverse Reactions | Prevalence of Opioid Poisoning | Direct Cost Estimate ($, millions) | Total Cost Estimate ($, millions) |
|---|---|---|---|---|---|
| A* | Yes | Yes | 550,705 | 1,756 | 20,439 |
| B | Yes | No | 773,254 | 2,673 | 21,413 |
| C | No | Yes | 590,533 | 2,444 | 20,722 |
| D | No | No | 813,501 | 3,291 | 21,699 |
| E | HCUP: ICD-9-CM Codes | | 144,993 | 816 | 18,842 |

*Base Case

The mean estimates for heroin and prescription opioids and associated confidence intervals obtained from the probabilistic sensitivity analysis are shown in Table 3.7. Incorporating the uncertainty from each of the inputs, the total direct, indirect, and combined costs were estimated to be $2.2 billion (95% CI = [1.3, 3.1]), $14.1 (95% CI = [14.0, 14.3] and $20.4 (95% CI = [19.4, 21.5]), respectively. The mean combined cost per poisoning case was estimated to be $38,968 (95% CI = [27,777, 58,239]).

**Table 3.7: Probabilistic Sensitivity Analysis on Direct, Indirect, and Combined Costs**

| | Mean Cost per Event | 95% CI | Total Cost (millions) | 95% CI (millions) |
|---|---|---|---|---|
| **Direct Costs** | | | | |
| Heroin | 3,263 | 2,431 - 4,477 | 434 | 262 - 612 |
| Prescription Opioid | 4,324 | 3,303 - 5,657 | 1,759 | 1,062 - 2,454 |
| All | 4,077 | 3,058 - 5,404 | 2,199 | 1,335 - 3,084 |
| **Indirect Costs** | | | | |
| Heroin | 32,330 | 21,792 - 51,034 | 4,155 | 4,108 - 4,231 |
| Prescription Opioid | 35,963 | 24,777 - 55,156 | 14,146 | 13,996 - 14,357 |
| All | 34,828 | 23,993 - 53,995 | 18,246 | 18,047 - 18,539 |
| **Combined Costs** | | | | |
| Heroin | 35,556 | 24,857 - 53,956 | 4,590 | 4,388 - 4,806 |
| Prescription Opioid | 40,232 | 28,816 - 59,654 | 15,895 | 15,112 - 16,724 |
| All | 38,968 | 27,777 - 58,239 | 20,443 | 19,443 - 21,471 |

This table displays the results of the probabilistic sensitivity analysis. Each mean value and associated 95% CI represents a separate set of 10,000 Monte Carlo simulations. Direct and indirect costs may not add up exactly to total costs as each value was created from a separate simulation.

## Section 3.3: Discussion

This is the first study that specifically evaluates the economic burden of opioid poisoning in the United States. Results from this analysis help define the scope of the problem and inform future economic evaluations of interventions intended to prevent or reverse opioid poisoning. This research illustrates that interventions seeking to reduce mortality by preventing and/or reversing opioid poisoning abusers can have the greatest economic benefits because mortality represented the largest percent of the total costs associated with opioid poisoning. In addition, prompt reversal of opioid poisoning through timely access to naloxone can potentially reduce medical costs by mitigating the severity of presentation and preventing complications related to prolonged hypoxia.

Although the use of naloxone in the outpatient setting has the potential to save lives, physicians may be reluctant to prescribe naloxone.[34] Nevertheless, initiatives across the country have sought to increase the availability of naloxone to caregivers, friends, or family members to intervene in the event of an acute opioid poisoning.[33] Though some programs have only focused efforts toward injection drug users[176-178], expert opinion and evidence supports expanding naloxone access to other populations such as high-risk users and abusers of prescription opioid analgesics.[179, 180]

Instead of measuring excess costs after an opioid poisoning event, such as in previous studies, costs directly associated with an opioid poisoning event were measured in this study. This is important because excess costs may include costs not only related to substance abuse treatment, but those related to treating medical complications and comorbidities. Because substance abusers are inherently more likely to engage in riskier behaviors compared to the

general population, these costs do not necessarily represent costs related to treating the substance abuse symptoms. Finally, heroin is included in these estimates in addition to prescription opioids in our analysis.

Costs for ED visits related to opioid poisoning were estimated to be $1,832. As a rough comparison, ED costs for all visits in 2003 was estimated to be approximately $408 in 2011 dollars [161]. Comparing across other injury types, our estimated mean cost for inpatient stays due to opioid poisoning ($9,723) was slightly lower than an estimate obtained from a previous report for hospital stays involving all injury related diagnoses ($10,300 in 2004) [181]. This is expected since other types of injury related diagnoses may involve different levels of trauma and may require a greater level of care.

When only direct costs were considered, prescription opioid analgesics had a greater average cost per poisoning event than heroin. This greater cost reflects the greater percentage of visits resulting in hospitalization for prescription opioids compared to heroin in the ED (18% vs. 27%) and the lower observed costs associated with the ED treatment of heroin. The lower costs for heroin in the ED may be due to the shorter half-life of heroin (8 to 22 minutes[63]) as compared to prescription opioid analgesics, which tend to have longer half-lives that vary by drug and formulation. The longer durations of action for prescription opioids may require longer monitoring periods and multiple naloxone administrations, resulting in greater resource utilization. In contrast, there was little difference in mean costs in the inpatient setting between opioid types. Once reaching a certain threshold of severity that necessitates admission, the presentation and management of prescription opioid and heroin poisoning and associated injuries may be similar. This contrasts with the ED setting where a greater variation of severity is expected.

Indirect costs contribute the largest percentage of the total burden of opioid poisoning. Mortality accounted for the great majority of the $20.4 billion total yearly cost; absenteeism accounted for just $335 million. The estimate of absenteeism costs serves as a lower bound as no caregivers for adults were assumed due to lack of data availability for caregiver burden among those who experience opioid poisoning. It is also noted that the average indirect cost per poisoning event was greater for prescription opioids than for heroin. This higher cost was largely driven by a larger number of mortality cases relative to ED visits or hospitalizations for prescription opioids than for heroin.

It is helpful to compare estimates obtained in this study with previous studies that evaluate costs in prescription opioid abuse. When evaluating prescription opioid abuse, the total costs in the most comprehensive study to date was approximately $55.7 billion.[37] Of this, $23.7 billion were attributed to excess medical and drug costs. Other yearly estimates of direct medical costs in opioid abuse were lower, between $2.2 and $2.6 billion.[36, 38] Differences in these estimates were due to the inclusion of caregiver medical burden and due to the addition of other sources of healthcare costs not included in studies with the lower estimates. In comparison, prescription opioids accounted for approximately $1.8 billion annually in direct costs related to the provision of care for patients that experienced opioid poisoning. Estimates obtained in our analysis are consistent with the previous studies evaluating the economic burden of opioid abuse as it is lower than the estimates obtained for direct costs in these previous studies. Estimates obtained in this study for prescription opioid poisoning mortality are similar to previous mortality estimates that evaluated costs related to opioid misuse and abuse.[37, 38] Only one study has previously attempted to apportion prescription opioid mortality costs to specific opioid analgesics.[38] In that study, mortality costs were apportioned based on prescription sales data and

reports of misuse according to the National Survey on Drug Use and Health (NSDUH). However, this assumes that each specific prescription opioid has the same likelihood of opioid poisoning mortality. In this study, mortality costs were apportioned based on estimates from the DAWN data, which may be a better reflection of the relative proportions of opioid analgesics implicated in opioid-related mortality compared to prescription sales data. One caveat should be mentioned with regards to interpreting the costs associated with methadone mortality compared to other prescription opioids. The proportion of methadone mentions is lower than that other prescription opioids (see Table 3.3). This discrepancy exists because the current estimates of methadone-related mortality are based on direct estimation of NVSS mortality data. To check why this discrepancy exists, the ratio of the weighted number of non-methadone prescription opioid ED mentions to non-methadone prescription opioid deaths was calculated and compared to the ratio of methadone visits to methadone-related deaths. The ratio of ED visits to deaths for non-methadone opioids was 43.1 to 1 where as for methadone it was 12.8 to 1, which may explain why mortality costs for methadone are higher compared to direct and indirect costs. In other words, there were more recorded methadone-related deaths per methadone-related ED visits than there were for non-methadone related prescription opioid deaths per non-methadone related prescription opioid deaths. Although this is a crude analysis, it may give a clue as to why this discrepancy was observed.

It is also helpful to compare total estimates obtained in this study with estimates for other conditions to provide context to the economic burden that opioid poisoning imposes on society. Diabetes, a commonly occurring chronic condition with high costs and significant long-term morbidity has been estimated to cost $218 billion in 2007.[182] Stroke, an acute condition with long-term morbidities for survivors, was estimated to have an economic burden of $65.5 billion

in terms of combined direct and indirect costs in 2008.[183] One should note of these conditions tend to have long-term complications unlike opioid poisoning which usually only have short-term consequences in uncomplicated cases. Another comparison can be drawn with food allergy and anaphylaxis. In a approach similar to the one used in this analysis, food allergies and anaphylaxis cost $340 million in 2007 in terms of direct costs from ED visits, outpatient visits, hospital runs, drug costs and indirect costs arising from absenteeism and premature mortality.[184] Indeed, opioid poisoning carries a significant economic burden to society and efforts to attenuate opioid poisoning should be a high priority. Several limitations exist with this analysis. First, only non-federal hospitals were considered when obtaining estimates of cost and prevalence; therefore, direct cost estimates do not apply to those receiving treatment at the Veterans Health Affairs Hospital System. However, the VHA system represents a relative small percent of all ED visits and inpatient stays. For example, the mean annual census for VHA emergency departments is 13,371.[185] In contrast, the total estimated number of ED visits in non-federal hospitals in 2009 was 128,885,040.[186] Second, defining opioid poisoning cases using currently available datasets results in several challenges. There is uncertainty with regards to the true prevalence of opioid poisoning in the United States. Using ICD-9-CM codes alone may underestimate opioid poisoning codes since model insurance policies do not extend liability for intoxication diagnoses to the insurer.[187] Physicians or coders may underreport these diagnoses to ensure coverage, which would lower prevalence estimates derived from ICD-9-CM codes. Hence, the DAWN database was used to measure prevalence since it captures all mentions of the implicated drug independent of the written diagnoses. This may be a more complete representation of all cases related to opioid poisoning. Although the possibility exists that non-poisoning cases are included in the DAWN prevalence estimates, the sample in the base case

scenario was limited to those patients not referred to or admitted to services/visits related to detoxification or psychiatric illness or who presented due to adverse reactions. Furthermore, this uncertainty was accounted for in the probabilistic sensitivity analysis, allowing for wide variation in the true prevalence of poisoning (+/- 50%).

Because treatment costs were estimated using ICD-9-CM codes, bias may exist if codes do not accurately reflect cases of opioid poisoning. For example, cases that result in physical injury indirectly associated with opioids may not be captured in the dataset as a poisoning case. Since diagnoses were not available in the DAWN dataset, costs were also estimated using the prevalence estimates derived from ICD-9-CM codes in the NEDS and NIS datasets. The prevalence of opioid poisoning was estimated to be lower than DAWN-derived estimates, at 128,788, or 42 per 100,000 population, with approximately 87% involving prescription opioids. This resulted in total costs of $18 billion per year compared with the estimated $20 billion in the base case analysis. The difference between total cost estimates is relatively small due to the large scale of mortality costs compared to other components of costs.

The costs per poisoning event assumes that all cases of poisoning resulted in either ED treatment, hospitalization, or death. This does not capture cases that resolve without medical treatment outside the hospital setting. Because of this possibility, the costs per poisoning event may be biased upwards. Additionally, the 95% confidence intervals obtained using the probabilistic sensitivity analysis for costs per poisoning event were wide. The wideness of the confidence intervals is due to the high sensitivity of this estimate to the calculated prevalence estimates along with the variation in the productivity reduction for the DPVs. When assuming lower prevalence estimates in the ED and inpatient settings, mortality costs get weighted more, and hence would increase the cost per poisoning event since mean mortality costs are greater

than direct costs. Similarly, assuming a higher prevalence in the ED and inpatient settings would result in a lower cost per poisoning event. Assuming a greater reduction in the DPV would lead to a lower cost per event, and vice versa.

To convert charges to costs in the inpatient setting, hospital specific CCRs were available to perform the conversion. Currently however, there are no standard procedures to convert ED charges to costs in the national HCUP NEDS data, requiring the use of summary CCRs published by HCUP in 2003.[161] The CCRs may have changed since 2003, but no further updates to these CCRs have ben provided. This may be a major limitation as evidence has suggested that ED reimbursement relative to ED charges decreased from 1996 to 2004 in the face of rising charges without parallel rises in total reimbursement.[188]

Cost data for specific opioid analgesics were not available in the HCUP datasets, so it was assumed that the mean treatment cost for poisoning was equal for each prescription opioid when apportioning costs. An exception was made for methadone, since mean treatment costs for methadone can be calculated separately using ICD-9-CM codes within the NIS and NEDS datasets. Second, apportionment of mortality costs to specific prescription opioids was based on ED and inpatient data. If there was a difference in the proportions of prescription opioids involved in the hospital setting from instances of opioid poisoning mortality outside the hospital setting, then results may be biased.

Finally, this study did not examine medical costs associated with prevention of poisoning or any downstream costs subsequent to the poisoning event. Costs of naloxone prescription programs, abuse education, and other efforts to prevent opioid poisoning were not examined. In addition, healthcare utilization after and beyond an opioid poisoning event was not evaluated. Indeed, a poisoning may be the first contact of many with the healthcare system and may result

in follow-up visits to address substance abuse issues and rehabilitation. One study in Medicaid patients found healthcare utilization and associated costs after opioid poisoning were almost $10,000 per year more compared to non-abusers.[39] In this study, the acute costs of opioid poisoning are provided, but further studies should evaluate downstream costs in both privately and publically insured populations.

# Chapter IV:

## Methods, Results and Discussion for Specific Aim II:

Evaluating differences in hospital costs, length of stay, and inpatient mortality between patients hospitalized for heroin, methadone, and non-methadone opioid analgesic poisoning

### Section 4.1: Methods

*Database & Sample Selection*

The HCUP NIS database in 2009 was used for this specific aim. This database has been described in Specific Aim I. The sample included all with an ICD-9-CM diagnosis of opioid poisoning (Table 3.1). Once the sample was identified, patients were categorized based on opioid type. To make direct comparisons between opioid types, it was necessary to produce mutually exclusive categories. All patients with a diagnosis of heroin poisoning were categorized as heroin patient. Next, all those with a diagnosis of methadone, but not heroin, were categorized as methadone patients. Finally, all other opioid poisoning diagnoses, with the exception of unspecified opioids were considered prescription opioids. Because of the uncertainty for the type of opioids that are involved with "unspecified" opioids, it was decided to separate out poisoning by opium (965.00, alkaloids, unspecified) to better distinguish between opioid types. For coding purposes, the ICD-9-CM code for '965.09' is used when specific opioids are identified. For the purposes of clarity in this specific aim, diagnoses for '965.09' will be referred to as "opioid analgesics" or "prescription opioids" and '965.00' will be referred to as "unspecified opioids".

Charges were transformed to reflect costs using hospital-specific cost-to-charge ratios and adjusted to 2011 U.S. dollars using the medical component of the CPI.[166] Patient and hospital characteristics by opioid type were reported. Unadjusted costs, LOS, and in-hospital mortality were also reported. Outcomes were adjusted based on patient characteristics, hospital characteristics, and Elixhauser comorbidities. Costs were additionally adjusted using the area wage index (AWI) to control for geographic area labor market differences in wages. Patient characteristics included age, sex, race and primary payer status. Hospital characteristics included urban/rural designation, teaching status, hospital bed size, ownership, and region. Elixhauser comorbidities included congestive heart failure, valvular disease, pulmonary circulation disorders, peripheral vascular disease, hypertension, other neurological disorders, chronic pulmonary disease, diabetes with complications, diabetes without complications, renal failure, liver disease, chronic peptic ulcer disease, HIV/AIDS, lymphoma, solid tumor without metastasis, rheumatoid arthritis/collagen vascular diseases, coagulation deficiency, obesity, blood loss anemia, deficiency anemias, drug abuse, psychoses, and depression.

*Sensitivity Analyses*

*Other comorbid conditions*

Adjustment of comorbidities using the Elixhauser method is a validated method of risk adjustment when evaluating outcomes. Although this method is validated, it is a general tool that may not adjust for all important comorbidities in specific conditions. Therefore, it was of interest to explore if other potential conditions aside from the included Elixhauser comorbidities were important in explaining costs, and if inclusion of these conditions are important when estimating adjusted costs associated with each opioid type. Specific conditions that were

evaluated are listed in Table 4.1 and were based on previous comorbidities evaluated in this population.[39] Comorbidities were evaluated for redundancy after cross-referencing these comorbidities with Elixhauser comorbidities (See Table 4.1) In the next step, the differences in the frequencies of these comorbidities were evaluated by drug type. Those comorbidities shown to vary by drug type were considered for further analyses. Bivariate analyses were done on the remaining comorbidities for costs, LOS, and mortality. Only ones that were significant in this step were entered into each of the models for the sensitivity analysis.

*Inclusion of Median Income by ZIP Code*

Because median income by ZIP code was not available for all states, it was decided to exclude median income as a covariate. This was included in a subsequent sensitivity analysis.

*Exclusion of Non-Poisoning DRGs*

The various outcomes were also compared between opioid types using DRGs related to poisoning. This was done because many other DRGs were observed in this analysis. Below in Table 4.2 are the top 10 DRGs observed in the sample. In the sensitivity analysis, only visits with DRGs 917 and 918 were included.

**Table 4.1: Specific Opioid Abuse-Related Comorbidities**

| Initial Comorbidities | Considered Comorbidites after Exclusions* |
|---|---|
| Sedative/hypnotic involvement | Sedative/hypnotic/anxiolytic involvement |
| Alcohol involvement | Alcohol involvement |
| Involvement of other drugs of abuse | Involvement of other drugs of abuse |
| Depression | Endocarditis |
| Anxiety | Skin infections |
| HIV/AIDS | Gastrointestinal bleed |
| Endocarditis | Pancreatitis |
| Skin infections | Sexually transmitted infection |
| Gastrointestinal bleed | Herpes simplex |
| Cirrhosis/chronic or acute liver disease | Burns |
| Hepatitis A,B, C | Trauma |
| Alcoholic hepatitis | Motor vehicle accidents |
| Other hepatitis | Back/neck pain |
| Pancreatitis | Acute pain NOS |
| Sexually transmitted disease | Chronic pain NOS |
| Herpes simplex | Neuropathic pain |
| Burns | Headache/migraine |
| Trauma | Suicide |
| Motor vehicle accidents | |
| Cancer | |
| Back/neck | |
| Arthritis | |
| Neuropathic pain | |
| Headache/migraine | |

*Exclusions were applied after cross-referencing against Elixhauser comorbidities and evaluating whether differences existed in the presence of these conditions by opioid type. For ICD-9-CM diagnoses used, see Appendix D.

**Table 4.2 Descriptions and Frequencies of Most Common DRGs**

| DRG Code | Description | Frequency | Percent |
|---|---|---|---|
| 918 | Poisoning & toxic effects of drugs without major complications | 5,696 | 41.7 |
| 917 | Poisoning & toxic effects of drugs with major complications | 5,089 | 37.25 |
| 885 | Psychoses | 452 | 3.31 |
| 208 | Respiratory system diagnosis with ventilator support | 178 | 1.3 |
| 871 | Septicemia or severe sepsis without mechanical ventilation | 135 | 1.0 |
| 897 | Alcohol/drug abuse or dependence without rehabilitation therapy without major complications | 112 | 0.8 |
| 999 | Ungroupable | 108 | 0.8 |
| 881 | Depressive neuroses | 107 | 0.8 |
| 4 | Percutaneous cardiovascular procedure with drug-eluting stent with major complications or 4+ vessels/stents | 57 | 0.4 |
| 907 | Other operating room procedures for injuries with major complications | 53 | 0.4 |

*Statistical Analysis*

Unadjusted estimates for inpatient costs, LOS, and in-hospital mortality were estimated for each of the separate opioid types (i.e., heroin, methadone, non-methadone opioid analgesics, and unspecified opioids). Bivariate analyses were conducted with each outcome by age, race, sex, primary payer status, and each of the hospital characteristics. Hospital characteristics included hospital bed size, teaching status, urban/rural status, hospital ownership and hospital region. Each bivariate analysis was conducted using Pearson's $\chi^2$ test. Under the assumption of the central limit theorem, ANOVA and t-tests were used to compare costs and LOS and costs between different characteristics.

Generalized linear models were fitted to the cost and LOS models. Mortality was estimated using logistic regression. Generalized linear models offer several key advantages over

ordinary least squares (OLS) regression. One of the key requirements for OLS regression is homoscedasticity; that is, variance of the error must be constant. However, as mean expenses increase, so does the variance, introducing heteroscedasticity.[189] To stabilize the variance, one can transform using the logarithm. This requires retransforming back to the original scale, which can introduce bias.[189] The gamma and inverse Gaussian distributions have been proposed to take into account distributional characteristics of expenditure data.[189]

To test the most appropriate distribution for costs and LOS, the Quasi-Likelihood under the independence model criterion (QIC) was employed. Robust standard errors were calculated in SAS by using PROC GENMOD with a REPEATED statement with an independent correlation matrix. This invokes a GEE procedure that reduces down to estimates produced by generalized linear models accounting for intra-hospital correlation within each hospital for each observation. The Akaike Information Criterion (AIC) is used to test model fit when using maximum likelihood estimation as in with generalized linear models. However, since GEE does not use maximum likelihood estimation, model fit was assessed using the 'Quasi-Likelihood under the independence model criterion' (QIC).[190]

It was also of interest to determine whether or not there was an increase in the intensity of healthcare utilization independent of LOS. To test this, hospital LOS was included as a regressor in the regression model assessing costs. This was also tested in a separate Poisson regression model, with number of procedures as the outcome variable, while controlling for LOS, patient characteristics, hospital characteristics, and Elixhauser comorbidities.

Costs were fitted using the gamma and inverse Gaussian distributions with a log-link. LOS was fitted using three different distributions, each with a log-link: log-normal, negative binomial, and a Poisson distribution. Models with the lowest QIC were chosen for the analyses.

The reference category for the opioids was for specified opiates (965.09). Other pairwise comparisons for opioid type were performed for the base case scenario only. Wald's $\chi^2$ test was used to compare between opioid types and a Bonferroni adjustment for additional pairwise comparisons was performed. An $\alpha$ level of 0.05 was used for all analyses. For additional pairwise comparisons (3 pairwise comparisons), an $\alpha$ of 0.017 was used. All statistical analyses were performed using SAS 9.3 (SAS Inc., Cary, NC). PROC GENMOD was used to model the generalized linear models and the logistic regression. The REPEATED statement was used to cluster visits by hospital and obtain robust standard errors. The LSMEANS statement was used to estimate adjusted costs.

## Section 4.2: Results

*Suspiciously High Charges and LOS*

Suspiciously high charges were identified prior to analyzing the data for costs. The methods for identifying suspiciously high charges have been previously described by HCUP (http://www.hcup-us.ahrq.gov/reports/statbriefs/sb97.jsp). To identify suspiciously high charges, the top 1% of charges per hospital day was identified. For the purposes of this calculation, all LOS values equal to 0 were set at a LOS of 1. The difference between the 75$^{th}$ percentile and the median of the top 1% was multiplied by 4 and added to the median. This value served as the threshold for suspiciously high charges for exclusion. When this was performed, three observations were identified and excluded from further analyses. The charges per day for these observations ranged from $112,859 and $160,084. As a conservative measure, the same procedure was applied to LOS. When this procedure was applied, 9 observations were excluded. The LOS for the excluded observations ranged from 88 to 211 days.

*Distributions for Costs and LOS*

Both costs and length of stay were highly skewed to the right. Costs ranged from $299 to $359,297 after excluding suspiciously high charges. The mean cost for the entire sample was $9,787 (SD = 14,536) and the median was $5,712 (IQR = [3,368 – 10,606]). The LOS ranged from 0 days to 82 days after excluding suspiciously high lengths of stay. The mean LOS was 3.9 days (SD = 5.03) and the median LOS was 2 days (IQR = [1 – 5]).

*Missing Data*

Length of stay was not missing for any of the eligible visits. Six-hundred thirty three eligible visits had missing cost information. The indicator for death was missing in 10 visits. Missing observations for costs and death by drug type are provided in the Table 4.3. Missing observations were excluded from the analysis.

**Table 4.3: Frequency of Missing Data**

| | Heroin | Prescription Opioid | Methadone |
|---|---|---|---|
| Costs | 109 (7.6%) | 436 (4.2%) | 88 (4.9%) |
| Died | 4 (0.3%) | 3 (0.2%) | 3 (0.03%) |

*Sample Characteristics by Opioid Type*

Sample demographics and hospital characteristics according to opioid type are presented in Table 4.4. For demographics, significant differences were found for age, sex, race and primary payer type. Those with heroin poisoning were younger compared to patients with prescription opioid or methadone poisoning. A majority of the patients in the heroin group were between the ages of 18 and 34 years of age. A plurality of patients in the methadone, prescription opioid, and unspecified opioid groups were between the ages of 35 and 54 years. Heroin patients were less likely to be female compared to all the other opioid groups. Compared to heroin poisoning patients, those with prescription opioid and methadone poisoning were more likely to be white. Patients with poisoning involving heroin were more likely to be black and Hispanic compared to the other groups. Compared to the other groups, the prescription opioid group had a lower percentage of Medicaid beneficiaries (19.2% vs. over 30% in other groups). There were a higher percentage of patients with Medicare as the primary payer among those with

prescription opioid and methadone poisoning compared to all other groups. A higher proportion in the prescription opioid group had private insurance compared to the other groups. Compared to the other opioid types, a higher proportion of visits with heroin poisoning had "self-pay" (i.e., uninsured) or "other" listed as the primary payer.

Differences in the distribution of hospital characteristics were also observed depending on opioid type. Most patients in all opioid categories were hospitalized in large hospitals. No differences were observed between opioid types with respect to hospital bed size. A majority of the heroin patients were hospitalized in teaching hospitals (58%) whereas the majority of visits in the other groups were in non-teaching hospitals. Approximately 96% percent of hospital stays involving heroin were in urban hospitals. Visits involving prescription opioids, methadone and unspecified opioids were less likely to be in urban hospitals (between 84% and 86%). Most of the patients were hospitalized in private, non-for-profit hospitals. The largest percentage of visits involving private not-for-profit hospitals was for heroin (74.7%) while the lowest was for methadone (67.7%). Those hospitalized in government-owned hospitals comprised a slightly larger percent of methadone patients (17.1%) compared to heroin (13.6%) or prescription opioid patients (12.9%). Regional variations were noted, with the largest percentage of heroin patients in the northeast region, while the largest percentage for the rest of the opioid groups were in the South.

Patients hospitalized for prescription opioid poisoning were less likely to be hospitalized in medium size hospitals (19.2%) compared to either heroin (28.5%) or methadone (27.9%). A larger share of heroin patients were hospitalized in teaching hospitals (58.0%) compared to either prescription opioid patients (38.7%) or methadone patients (45.3%). Heroin patients were also more likely to be hospitalized in urban hospitals (95.7%) than prescription opioid patients

(84.3%) or methadone patients (85.9%). A larger percentage of heroin patients were hospitalized in private not-for-profit hospitals (74.6%) compared to the other categories (70.7% for prescription opioids and 67.2% for methadone). Methadone patients were more likely to be hospitalized in a government hospital (17.4%) compared to either heroin (13.7%) or prescription opioid patients (13.3%). Finally, a smaller percentage of heroin patients 17.6% were hospitalized in the south compared to the other categories (41.9% and 35.1%).

*Costs, LOS, and Mortality by Patient and Hospital Characteristics*

Older age was significantly associated with greater costs and length of stay. Those over the age of 65 had a mean cost of $11,323 and a LOS of 4.9 days while those less than 18 years of age had a mean cost of $6,481 and a LOS of 2.5 days. Though a positive trend was observed with mortality and age, there were no significant differences. Males were observed to have a higher cost than females, but the difference was not significant. Differences between sexes were not observed with regards to LOS. Males, however, did have a statistically significantly greater likelihood of mortality compared to females (3.2% vs. 2.4%). Differences were not observed in costs or mortality between race categories. However, differences were observed with regards to LOS. Blacks had the longest LOS (4.3 days) while Asians/Pacific Islanders had the shortest (3.3 days). Significant differences were observed with respect to payer type in costs, LOS, and inpatient mortality. Patients with Medicare and Medicaid had the greatest costs ($10,752 and $10,705, respectively) compared to all other payer types. Mean LOS was greater for visits involving Medicare and Medicaid (4.5 and 4.0 days, respectively).

All hospital categories were observed to have significant differences in costs. Medium and large hospitals ($9,946 and $9,897, respectively) were shown to have greater mean costs

than small hospitals. The same trend was observed for length of stay with medium and large hospitals (3.7 and 4.2 days, respectively) having a greater man LOS than small hospitals (3.4 days), though no differences were observed with respect to mortality. Teaching hospitals were also shown to have greater costs and LOS than non-teaching hospitals ($10,704 and $9,148, respectively and 4.5 and 3.6 days, respectively). No differences in mortality were observed between teaching and non-teaching status. Though patients in urban hospitals had higher costs than in rural hospitals ($10,235 vs. $7,127), they had a lower LOS than in rural hospitals (2.9 vs. 4.2 days). Private not-for-profit hospitals were associated with the greatest mean cost ($9,990) while private, for-profit hospitals were associated with the least ($8,978). Hospitals in the western and northeastern regions of the U.S. had the greatest costs ($12,187 and $11,183, respectively) while those in the southern and Midwestern regions had the lowest costs ($8,588 and $8,676, respectively).

**Table 4.4: Patient and Hospital Characteristics by Opioid Type**

| | Heroin (%) | Methadone (%) | Prescription Opioid (%) | Unspecified (%) | p-value ($\chi^2$) |
|---|---|---|---|---|---|
| Age | | | | | |
| < 18 | 20 (1.4) | 48 (2.9) | 195 (2.9) | 94 (2.5) | |
| 18 – 34 | 751 (53.3) | 499 (29.6) | 1,485 (22.2) | 887 (23.8) | < 0.0001 |
| 35 – 54 | 518 (36.7) | 746 (44.2) | 2,732 (40.8) | 1,701 (45.6) | (862.8) |
| 55 – 64 | 105 (7.5) | 290 (17.2) | 1,206 (18.0) | 683 (18.3) | |
| > 65 | 16 (1.1) | 104 (6.2) | 1,079 (16.1) | 368 (9.9) | |
| Female (%) | 368 (26.1) | 796 (46.9) | 3,910 (57.7) | 2,080 (55.2) | < 0.0001 (499.2) |
| Race (%) | | | | | |
| White | 872 (70.3) | 1,168 (79.6) | 4,916 (84.3) | 2,562 (80.2) | |
| Black | 170 (13.7) | 97 (6.6) | 392 (6.7) | 277 (8.7) | |
| Hispanic | 134 (10.8) | 93 (6.3) | 312 (5.4) | 188 (5.9) | < 0.0001 |
| Asian/P.I. | 16 (1.3) | 33 (2.3) | 108 (1.9) | 58 (1.8) | (205.0) |
| Other | 49 (4.0) | 77 (5.3) | 107 (1.8) | 109 (3.4) | |
| Primary payer | | | | | |
| Medicare | 121 (8.6) | 459 (17.2) | 2,380 (35.2) | 886 (23.6) | |
| Medicaid | 448 (31.9) | 521 (30.8) | 1,295 (19.2) | 1,138 (30.3) | |
| Private | 260 (18.5) | 266 (15.7) | 1,868 (27.6) | 890 (23.7) | < 0.0001 |
| No Charge | 41 (2.9) | 31 (1.8) | 78 (1.2) | 46 (1.2) | (866.2) |
| Self-Pay | 470 (33.5) | 343 (20.3) | 848 (12.5) | 617 (16.4) | |
| Other | 64 (4.6) | 70 (4.1) | 292 (4.3) | 179 (4.8) | |
| Hospital Bed Size | | | | | |
| Small | 151 (10.7) | 170 (10.2) | 793 (12.0) | 419 (11.4) | 0.0868 |
| Medium | 402 (28.6) | 451 (27.1) | 1,678 (25.3) | 945 (25.7) | (11.1) |
| Large | 854 (60.7) | 1,042 (62.7) | 4,166 (62.8) | 2,318 (63.0) | |
| Teaching Status | | | | | |
| Non-teaching | 591 (42.0) | 905 (54.4) | 4,187 (63.1) | 2,135 (58.0) | < 0.0001 |
| Teaching | 816 (58.0) | 758 (45.6) | 2,450 (36.9) | 1,547 (42.0) | (226.8) |
| Urban/rural Status | | | | | |
| Urban | 1,352 (95.9) | 1,461 (86.0) | 5,682 (83.8) | 3,213 (85.2) | < 0.0001 |
| Rural | 58 (4.1) | 238 (14.0) | 1,101 (16.2) | 557 (14.8) | (140.8) |
| Hospital Ownership | | | | | |
| Government | 191 (13.6) | 284 (17.1) | 854 (12.9) | 525 (14.3) | < 0.0001 |
| Private, NFP | 1,051 (74.7) | 1,125 (67.7) | 4,652 (70.1) | 2,632 (71.5) | (50.5) |
| Private, FP | 165 (11.7) | 254 (15.3) | 1,131 (17.0) | 525 (14.3) | |
| Region | | | | | |
| West | 291 (20.6) | 439 (25.8) | 1,543 (22.8) | 764 (20.3) | |
| Northeast | 467 (33.1) | 354 (20.8) | 950 (14.0) | 642 (17.0) | < 0.0001 |
| Midwest | 404 (18.7) | 314 (18.5) | 1,444 (21.3) | 801 (21.3) | (508.1) |
| South | 248 (17.6) | 592 (34.8) | 2,846 (42.0) | 1,563 (41.5) | |

NFP = not for profit; FP = for profit

**Table 4.5: Mean Costs by Patient & Hospital Characteristics**

| | Mean Costs (SD) | Test statistic | p-value |
|---|---|---|---|
| Age | | | |
| < 18 | 6,481 (14,622) | | |
| 18 – 34 | 7.942 (12,631) | $F_{4,12890} = 33.9$ | < 0.0001 |
| 35 – 54 | 9,907 (15,583) | | |
| 55 – 64 | 11,817 (14,851) | | |
| > 65 | 11,323 (13,936) | | |
| Sex | | | |
| Male | 10,043 (15,319) | t = 1.83 | 0.067 |
| Female | 9,571 (13,816) | | |
| Race | | | |
| White | 9,922 (15,071) | | |
| Black | 10,307 (15,830) | | |
| Hispanic | 11,337 (16,045) | $F_{4, 11106} = 1.53$ | 0.1914 |
| Asian/P.I. | 9,552 (14,272) | | |
| Other | 10,064 (16,612) | | |
| Primary payer | | | |
| Medicare | 10,752 (13,177) | | |
| Medicaid | 10,705 (19,384) | $F_{5, 12973} = 16.03$ | < 0.0001 |
| Private | 9,399 (13,535) | | |
| No Charge | 8,294 (11,713) | | |
| Self-Pay | 7,728 (10,930) | | |
| Other | 9,118 (10,370) | | |
| Hospital Bed Size | | | |
| Small | 8,818 (11,957) | | |
| Medium | 9,946 (14,251) | $F_{2, 12752} = 3.69$ | 0.0251 |
| Large | 9,897 (15,052) | | |
| Teaching Status | | | |
| Non-teaching | 9,148 (12,801) | $t_{12753} = -5.96$ | < 0.0001 |
| Teaching | 10,704 (16,654) | | |
| Urban/rural Status | | | |
| Rural | 7,127 (7,961) | $T_{4525} = 13.22$ | < 0.0001 |
| Urban | 10,235 (15,322) | | |
| Hospital Ownership | | | |
| Government | 9,693 (14,868) | | |
| Private, not for profit | 9,990 (14,502) | $F_{2,12752} = 4.04$ | < 0.0176 |
| Private, for profit | 8,978 (14,279) | | |
| Region | | | |
| West | 12,187 (17,112) | | |
| Northeast | 11,183 (17,038) | $F_{3,13024} = 50.54$ | < 0.0001 |
| Midwest | 8,676 (12,723) | | |
| South | 8,588 (12,650) | | |

ANOVA and t-tests were used for comparisons, where appropriate.

**Table 4.6: Mean LOS by Patient Characteristics**

| | Mean LOS (SD) | Test statistic | p-value |
|---|---|---|---|
| Age | | | |
| < 18 | 2.47 (3.80) | | |
| 18 – 34 | 3.16 (4.73) | $F_{4,13513} = 59.0$ | < 0.0001 |
| 35 – 54 | 3.82 (4.86) | | |
| 55 – 64 | 4.76 (5.81) | | |
| > 65 | 4.86 (5.01) | | |
| Sex | | | |
| Male | 3.89 (5.30) | t = 0.05 | 0.9635 |
| Female | 3.89 (4.78) | | |
| Race | | | |
| White | 3.90 (5.08) | | |
| Black | 4.31 (6.05) | $F_{4,11724} = 2.4$ | 0.0481 |
| Hispanic | 4.14 (5.02) | | |
| Asian/P.I. | 3.31 (3.93) | | |
| Other | 3.96 (5.80) | | |
| Primary payer | | | |
| Medicare | 4.51 (4.96) | | |
| Medicaid | 4.02 (5.75) | | |
| Private | 3.66 (4.94) | $F_{4,13601} = 28.6$ | < 0.0001 |
| No Charge | 3.85 (5.97) | | |
| Self-Pay | 3.02 (4.08) | | |
| Other | 3.54 (4.10) | | |
| Hospital Bed Size | | | |
| Small | 3.36 (6.71) | | |
| Medium | 3.71 (4.97) | $F_{2,13386} = 16.2$ | < 0.0001 |
| Large | 4.21 (6.64) | | |
| Teaching Status | | | |
| Non-teaching | 3.62 (5.20) | $t_{13387} = 7.77$ | < 0.0001 |
| Teaching | 4.48 (7.48) | | |
| Urban/rural Status* | | | |
| Rural | 4.17 (6.62) | $t_{1953} = 14.23$ | < 0.0001 |
| Urban | 2.85 (3.08) | | |
| Hospital Ownership | | | |
| Government | 3.79 (5.22) | | |
| Private, not for profit | 4.02 (6.59) | $F_{2,13386} = 1.00$ | 0.3691 |
| Private, for profit | 3.97 (5.54) | | |
| Region | | | |
| West | 4.04 (6.65) | | |
| Northeast | 4.46 (6.62) | $F_{3,13658} = 9.25$ | < 0.0001 |
| Midwest | 3.56 (4.58) | | |
| South | 3.97 (6.65) | | |

ANOVA and t-tests were used for comparisons, where appropriate. Unequal variance t-test was used instead for urban/rural status

**Table 4.7: In-hospital Mortality by Patient & Hospital Characteristics**

| | n (%) | $\chi^2$ | p-value |
|---|---|---|---|
| Age | | | |
| < 18 | 5 (1.4) | | |
| 18 – 34 | 103 (2.9) | 8.68 | 0.07 |
| 35 – 54 | 154 (2.7) | | |
| 55 – 64 | 58 (2.5) | | |
| > 65 | 59 (3.8) | | |
| Sex | | | |
| Male | 206 (3.2) | 6.89 | 0.0087 |
| Female | 174 (2.4) | | |
| Race | | | |
| White | 279 (2.9) | | |
| Black | 23 (2.5) | 1.54 | 0.8193 |
| Hispanic | 21 (2.9) | | |
| Asian/P.I. | 6 (2.8) | | |
| Other | 7 (2.1) | | |
| Primary payer | | | |
| Medicare | 110 (2.7) | | |
| Medicaid | 113 (3.6) | | |
| Private | 70 (2.1) | 15.86 | 0.0072 |
| No Charge | 9 (4.6) | | |
| Self-Pay | 58 (2.6) | | |
| Other | 16 (2.7) | | |
| Hospital Bed Size | | | |
| Small | 37 (2.4) | 1.42 | 0.4901 |
| Medium | 92 (2.7) | | |
| Large | 243 (2.9) | | |
| Teaching Status | | | |
| Non-teaching | 202 (2.6) | 2.66 | 0.1028 |
| Teaching | 170 (3.1) | | |
| Urban/rural Status | | | |
| Rural | 341 (2.9) | 5.24 | 0.0221 |
| Urban | 39 (2.0) | | |
| Hospital Ownership | | | |
| Government | 52 (2.8) | | |
| Private, not for profit | 255 (2.7) | 1.21 | 0.5461 |
| Private, for profit | 65 (3.1) | | |
| Region | | | |
| West | 110 (3.6) | | |
| Northeast | 60 (2.5) | 11.36 | 0.0099 |
| Midwest | 68 (2.3) | | |
| South | 142 (2.7) | | |

Pearson's $\chi^2$ test was used for comparisons.

*Model Fit for Costs LOS Specifications*

Model fit for the cost LOS models were assessed with the QIC for the base case models. The QIC for the Poisson, negative binomial, and gamma distributions were -9781, -40,649, and 55,102, respectively. The QIC for the gamma and inverse Gaussian distributions were 192,057 and -10,252, respectively. Therefore, the Poisson distribution was assigned to the LOS models and the inverse Gaussian distribution was assigned to the cost models.

*Findings from Regression Models*

Unadjusted outcomes are shown in Table 4.8. Mean costs were greatest for methadone, followed by unspecified opioids, heroin, and prescription opioids. LOS was greatest for methadone and unspecified opioids, and lowest for prescription opioids. Mortality was greatest for heroin and lowest for unspecified opioids and methadone.

Adjusted outcomes are given in Table 4.9. After adjusting for covariates, significant differences were observed with respect to opioid type with each of the outcomes. Pairwise tests for opioid type were performed with the regression model coefficients in a subsequent step. Methadone was associated with the highest costs ($9,996), followed by unspecified opioids ($9,455), heroin ($9,279) and prescription opioids ($8,131). The adjusted LOS was highest for methadone at 3.8 days, followed by heroin (3.7), unspecified opioids (3.6) and prescription opioids (3.5). The adjusted probability of death was highest for heroin (2.1%), followed by unspecified opioids (1.4%), methadone (1.1%) and prescription opioids (0.9%).

**Table 4.8 Unadjusted Costs, LOS, and In-hospital Mortality**

| | Cost (95% CI) | LOS (95% CI) | Mortality* (95% CI) |
|---|---|---|---|
| Heroin | 10,182 (9,091 to 11,405) | 3.9 (3.6 to 4.3) | 4.9% (3.7% to 6.4%) |
| Methadone | 10,766 (9,803 to 11,823) | 4.2 (3.9 to 4.6) | 2.5% (1.8% to 3.4%) |
| Rx Opioid** | 9,154 (8,703 to 9,629) | 3.8 (3.7 to 4.0) | 3.3% (2.8% to 3.9%) |
| Unspecified | 10,361 (9,769 to 10,988) | 4.2 (3.9 to 4.5) | 2.3% (2.0% to 2.7%) |

Results are different from mean estimates from Specific Aim I since this analysis does not take into account sample design variables and also due to multiple imputation procedures performed in Specific Aim I.
* Unadjusted probability of death; ** Rx = prescription

**Table 4.9 Adjusted Costs, LOS, and In-hospital Mortality**

| | Cost (95% CI) | LOS (95% CI) | Mortality* (95% CI) |
|---|---|---|---|
| Heroin | 9,279 (8,563 to 10,055) | 3.7 (3.3 to 4.0) | 2.1% (1.2% to 3.5%) |
| Methadone | 9,996 (9,260 to 10,792) | 3.8 (3.6 to 4.1) | 1.1% (0.7% to 1.9%) |
| Rx Opioid** | 8,131 (7,844 to 8,428) | 3.5 (3.4 to 3.6) | 0.9% (0.6% to 1.4%) |
| Unspecified | 9,455 (8,984 to 9,951) | 3.6 (3.5 to 3.8) | 1.4% (0.9% to 2.2%) |

* Adjusted probability of death; ** Rx = prescription

*Costs*

The total number of observations in the cost model was 12,751. The output for the regression model is provided in Table 4.10. The coefficients in the model are referenced to those who have non-methadone opioid analgesic poisoning, are less than 18 years of age, male, white, have a private payer as primary payer status, or who are hospitalized in a small government-owned hospital in the West. Heroin, methadone, and unspecified opioids had 1.14 (95% CI = [1.05 to 1.24]), 1.23 (95% CI = [1.13 to 1.34]) and 1.16 (95% CI = [1.11 to 1.22]) times greater costs than prescription opioids, respectively. Other pairwise comparisons by opioid type were not significant.

Increases in age were associated with greater costs. Those older than age 65 had 1.48 (95% CI = [1.31 to 1.68]) times greater costs than those less than 18 years of age. Females had

costs 11% (95% CI = [8% to 15%]) lower compared to males. Interestingly, visits in which "self-pay" was the designated primary payer status had lower costs compared to visits in which private payers were listed ($\exp(\beta) = 0.86$, 95% CI = [0.80 to 0.91]). Asian ethnicity was associated with decreased costs compared to whites. The Midwest region was associated with 10% lower costs compared to the west.

**Table 4.11: Parameter Estimates from Costs Regression Model**

| Parameter | β | SE | Exp(β) (95% CI) | Z | p-value |
|---|---|---|---|---|---|
| Intercept | 7.578 | 0.215 | | 99.80 | < 0.0001 |
| Opioid Type | | | | | |
| RxO* | -- | -- | -- | -- | -- |
| Heroin | 0.132 | 0.042 | 1.14 (1.05 to 1.24) | 3.17 | 0.0015 |
| Methadone | 0.207 | 0.043 | 1.23 (1.13 to 1.34) | 4.85 | < 0.0001 |
| Unspecified | 0.151 | 0.025 | 1.16 (1.11 to 1.22) | 6.07 | < 0.0001 |
| Age Group | | | | | |
| < 18* | -- | -- | -- | -- | -- |
| 18 to 34 | 0.124 | 0.054 | 1.13 (1.02 to 1.26) | 2.31 | 0.0211 |
| 35 to 54 | 0.240 | 0.054 | 1.27 (1.14 to 1.41) | 4.45 | < 0.0001 |
| 55 to 64 | 0.366 | 0.060 | 1.44 (1.28 to 1.62) | 6.11 | < 0.0001 |
| > 65 | 0.393 | 0.065 | 1.48 (1.31 to 1.68) | 6.08 | < 0.0001 |
| Sex | | | | | |
| Male* | -- | -- | -- | -- | -- |
| Female | -0.122 | 0.021 | 0.89 (0.85 to 0.92) | -5.70 | < 0.0001 |
| Race | | | | | |
| White* | -- | -- | -- | -- | -- |
| Black | -0.121 | 0.053 | 0.89 (0.80 to 0.98) | -2.30 | 0.0217 |
| Hispanic | 0.079 | 0.069 | 1.08 (0.95 to 1.24) | -1.14 | 0.2532 |
| Asian | -0.207 | 0.099 | 0.81 (0.67 to 0.99) | 1.14 | 0.0367 |
| Other Race | -0.020 | 0.0762 | 0.98 (0.84 to 1.14) | -0.27 | 0.7899 |
| Payer | | | | | |
| Private* | -- | -- | -- | -- | -- |
| Medicare | 0.001 | 0.028 | 1.00 (0.95 to 1.06) | 0.04 | 0.9719 |
| Medicaid | 0.058 | 0.032 | 1.06 (0.99 to 1.13) | 1.79 | 0.0738 |
| Self-pay | -0.155 | 0.033 | 0.86 (0.80 to 0.91) | -4.69 | < 0.0001 |
| No Charge | 0.01 | 0.082 | 1.01 (0.86 to 1.19) | 0.12 | 0.9021 |
| Other | 0.0014 | 0.048 | 1.00 (0.91 to 1.10) | 0.03 | 0.9773 |
| Urban/Rural | | | | | |
| Urban | -- | -- | -- | -- | -- |
| Rural | -0.002 | 0.046 | 1.00 (0.91 to 1.09) | -0.05 | 0.959 |
| Hospital Bed Size | | | | | |
| Small bed* | -- | -- | -- | -- | -- |
| Medium bed | 0.050 | 0.055 | 1.05 (0.94 to 1.17) | 0.91 | 0.3623 |
| Large bed | 0.028 | 0.051 | 1.03 (0.93 to 1.14) | 0.54 | 0.5894 |
| Teaching Status | | | | | |
| Non-teaching* | -- | -- | -- | -- | -- |
| Teaching | 0.094 | 0.034 | 1.10 (1.03 to 1.17) | 2.80 | 0.0051 |
| Hospital Ownership | | | | | |
| Government* | -- | -- | -- | -- | -- |
| Private, non-profit | 0.034 | 0.049 | 1.03 (0.94 to 1.14) | 0.69 | 0.4891 |
| Private, for profit | -0.030 | 0.061 | 0.97 (0.86 to 1.09) | -0.50 | 0.6182 |
| Hospital Region | | | | | |
| West* | -- | -- | -- | -- | -- |
| Northeast | -0.076 | 0.057 | 0.93 (0.83 to 1.04) | -1.33 | 9.1828 |
| Midwest | -0.167 | 0.052 | 0.90 (0.81 to 1.00) | -3.21 | 0.0013 |
| South | -0.104 | 0.054 | 0.90 (0.81 to 1.00) | -1.92 | 0.0553 |
| Area wage index | 0.959 | 0.172 | 2.61 (1.86 to 3.66) | 5.56 | < 0.0001 |

Parameter estimates for Elixhauser comorbidities are found in Appendix C.

**Table 4.12: Additional Pairwise Comparisons for Costs**

| | exp(β) (SE) | 95% CI | Wald's $\chi^2$ | p-value |
|---|---|---|---|---|
| Met vs. Her | 0.91 (0.043) | 0.82 to 1.02 | 3.87 | 0.05 |
| Met. vs. Unsp | 1.02 (0.037) | 0.93 to 1.11 | 0.21 | 0.650 |
| Her vs. Unsp | 0.93 (0.038) | 0.84 to 1.02 | 3.41 | 0.065 |

Met = methadone; Her = heroin; Unsp = unspecified. Adjusted $\alpha = 0.017$

*Length of Stay*

A total of 13,376 observations were used in the LOS model. There were no significant differences observed between heroin and prescription opioids. Methadone was associated with a 10% (95% CI = [2% to 19%]) increase in LOS compared to prescription opioids. No other differences were observed between opioid types. Parameter estimates are shown in Table 4.13.

Older age was associated with increased length of stay, especially among those 35 years and older (See Table 4.13). Visits with "self-pay" as the designated primary payer were associated with a 13% lower LOS compared to those with a private payer (95% CI = [7% to 18%]). Visits in teaching hospitals had a 12% (95% CI = [5% to 20%]) greater LOS compared to visits in non-teaching hospitals. Visits in rural hospitals had 22% (95% CI = [15% to 28%]) lower LOS compared to visits in urban hospitals. Compared to visits in small hospitals, visits in medium and large bed hospitals had a 13% (95% CI = [3% to 24%]) and 28% (95% CI = [18% to 40%]) greater LOS, respectively. Compared to visits in hospitals from the western United States, visits in hospitals in the northeast had a 22% (95% CI = [11% to 35%]) greater LOS.

**Table 4.13: Parameter Estimates from LOS Regression Model**

| Parameter | β | SE | Exp(β) (95% CI) | Z | p-value |
|---|---|---|---|---|---|
| Intercept | 0.6769 | 0.0907 | 1.97 (1.65 to 2.35) | 7.46 | < 0.0001 |
| Opioid Type | | | | | |
| RxO* | -- | -- | -- | -- | -- |
| Heroin | 0.050 | 0.0512 | 1.05 (0.95 to 1.16) | 0.56 | 0.5777 |
| Methadone | 0.096 | 0.0399 | 1.10 (1.02 to 1.19) | 1.61 | 0.0162 |
| Unspecified | 0.046 | 0.0248 | 1.05 (1.00 to 1.10) | 1.87 | 0.0609 |
| Age Group | | | | | |
| < 18* | -- | -- | -- | -- | -- |
| 18 to 34 | 0.060 | 0.0670 | 1.06 (0.93 to 1.21) | 0.90 | 0.3707 |
| 35 to 54 | 0.159 | 0.0662 | 1.17 (1.03 to 1.34) | 2.40 | 0.0162 |
| 55 to 64 | 0.256 | 0.0690 | 1.29 (1.13 to 1.48) | 3.71 | 0.0002 |
| > 65 | 0.297 | 0.0718 | 1.35 (1.17 to 1.55) | 4.14 | < 0.0001 |
| Sex | | | | | |
| Male* | -- | -- | -- | -- | -- |
| Female | -0.030 | 0.0228 | 0.97 (0.93 to 1.02) | -1.3 | 0.193 |
| Race | | | | | |
| White* | -- | -- | -- | -- | -- |
| Black | -0.055 | 0.0513 | 0.95 (0.86 to 1.05) | -1.08 | 0.2808 |
| Hispanic | 0.026 | 0.0482 | 1.03 (0.93 to 1.13) | 0.54 | 0.5893 |
| Asian | -0.114 | 0.0813 | 0.89 (0.76 to 1.05) | -1.41 | 0.1599 |
| Other Race | -0.050 | 0.1080 | 0.95 (0.81 to 1.11) | -0.62 | 0.5350 |
| Payer | | | | | |
| Private* | -- | -- | -- | -- | -- |
| Medicare | 0.031 | 0.0286 | 1.03 (0.98 to 1.09) | 1.09 | 0.2754 |
| Medicaid | 0.051 | 0.0327 | 1.05 (0.99 to 1.12) | 1.55 | 0.1222 |
| Self-pay | -0.141 | 0.0326 | 0.87 (0.82 to 0.93) | -4.32 | < 0.0001 |
| No Charge | 0.100 | 0.1138 | 1.11 (0.88 to 1.38) | 0.88 | 0.3776 |
| Other | -0.018 | 0.0490 | 0.98 (0.89 to 1.08) | -0.37 | 0.7084 |
| Teaching Status | | | | | |
| Non-teaching* | -- | -- | -- | -- | -- |
| Teaching | 0.116 | 0.0326 | 1.12 (1.05 to 1.20) | 3.56 | 0.0004 |
| Urban/Rural | | | | | |
| Urban | -- | -- | -- | -- | -- |
| Rural | -0.247 | 0.0419 | 0.78 (0.72 to 0.85) | -5.9 | < 0.0001 |
| Hospital Bed Size | | | | | |
| Small bed* | -- | -- | -- | -- | -- |
| Medium bed | 0.120 | 0.0473 | 1.13 (1.03 to 1.24) | 2.54 | 0.0111 |
| Large bed | 0.252 | 0.0432 | 1.28 (1.18 to 1.40) | 5.83 | < 0.0001 |
| Hospital Ownership | | | | | |
| Government* | -- | -- | -- | -- | -- |
| Private, non-profit | -0.046 | 0.0472 | 0.96 (0.87 to 1.05) | -0.97 | 0.3325 |
| Private, for profit | 0.049 | 0.0609 | 1.05 (0.93 to 1.18) | 0.81 | 0.4206 |
| Hospital Region | | | | | |
| West* | -- | -- | -- | -- | -- |
| Northeast | 0.202 | 0.0493 | 1.22 (1.11 to 1.35) | 4.09 | < 0.0001 |
| Midwest | -0.049 | 0.0443 | 0.95 (0.87 to 1.04) | -1.10 | 0.5531 |
| South | 0.024 | 0.0396 | 1.02 (0.95 to 1.11) | 0.59 | 0.7646 |

Parameter estimates for Elixhauser comorbidities are found in Appendix C.

**Table 4.14: Additional Pairwise Comparisons for LOS**

| | exp(β) (SE) | 95% CI* | Wald's $\chi^2$ | p-value |
|---|---|---|---|---|
| Met vs. Her | 1.05 (0.055) | 0.92 to 1.19 | 0.72 | 0.3959 |
| Met. vs. Unsp | 1.05 (0.042) | 0.95 to 1.16 | 1.40 | 0.2373 |
| Her vs. Unsp | 1.00 (0.053) | 0.88 to 1.14 | 0.00 | 0.9532 |

Met = methadone; Her = heroin; Unsp = unspecified. Adjusted $\alpha = 0.017$

*In-hospital Mortality*

A total of 11,351 visits were included in this analysis. Results for the regression are found in Table 4.15. Patients with heroin poisoning had 2.3 times (95% CI = [1.5 to 3.5]) greater odds of in-hospital mortality compared to patients with non-methadone opioid analgesic poisoning. Heroin also had 1.8 times (95% CI = [1.12 to 2.95]) greater odds of in-hospital mortality than methadone. Significant differences were not observed between methadone and non-methadone opioid analgesics. Compared to prescription opioids, patients with unspecified opioid poisoning had a 1.5 (95% CI = [1.2 to 2.0]) times greater odds of death. Compared to heroin, methadone was associated with a 45% (95% CI = [1% to 69%]) lower odds of mortality.

Compared to those less than 18 years of age, those in the '18 to 34' and '35 to '54' age group were 3.0 times greater odds of experiencing in-hospital mortality (95% CI = [1.0, 8.9]). Those greater than age 65 had 4.0 times (95% CI = [1.3, 12.8]) greater odds of in-hospital mortality compared to those less than 18 years of age. No differences were observed with respect to race when compared to whites. Females were 22% (95% CI = [1% 39%]) lower odds of in-hospital compared with males. When compared with private payers, patients with Medicaid had 1.95 times (95% CI = [1.35 to 2.81]) greater odds of mortality. When compared to small bed sizes, no significant differences were observed with respect to medium and large bed

hospitals. There were also no significant differences between government-owned hospitals and privately-owned hospitals.

**4.15: Odds Ratios from Mortality Regression Model**

| Parameter | OR | SE | 95% CI | $\chi^2$ | p-value |
|---|---|---|---|---|---|
| Opioid Type | | | | | |
| RxO* | -- | -- | -- | -- | -- |
| Heroin | 2.28 | 0.489 | 1.50 to 3.47 | 14.8 | 0.0151 |
| Methadone | 1.25 | 0.258 | 0.84 to 1.88 | 1.21 | 0.2722 |
| Unspecified | 1.53 | 0.213 | 1.16 to 2.01 | 9.23 | 0.0024 |
| Age Group | | | | | |
| < 18* | -- | -- | -- | -- | -- |
| 18 to 34 | 3.03 | 1.6668 | 1.03 to 8.90 | 4.09 | 0.0432 |
| 35 to 54 | 3.02 | 1.6633 | 1.03 to 8.89 | 4.04 | 0.0443 |
| 55 to 64 | 2.36 | 1.3427 | 0.77 to 7.20 | 2.28 | 0.1307 |
| > 65 | 4.01 | 2.3721 | 1.26 to 12.78 | 5.51 | 0.0189 |
| Sex | | | | | |
| Male* | -- | -- | -- | -- | -- |
| Female | 0.78 | 0.0961 | 0.61 to 0.99 | 4.05 | 0.0442 |
| Race | | | | | |
| White* | -- | -- | -- | -- | -- |
| Black | 0.71 | 0.1748 | 0.44 to 1.15 | 1.90 | 0.1680 |
| Hispanic | 0.80 | 0.2048 | 0.49 to 1.32 | 0.75 | 0.3872 |
| Asian | 0.89 | 0.3265 | 0.44 to 1.83 | 0.10 | 0.7562 |
| Other Race | 0.66 | 0.2281 | 0.33 to 1.30 | 1.47 | 0.2247 |
| Payer | | | | | |
| Private* | -- | -- | -- | -- | -- |
| Medicare | 1.15 | 0.233 | 0.77 to 1.71 | 0.48 | 0.4873 |
| Medicaid | 1.95 | 0.363 | 1.35 to 2.81 | 12.78 | 0.0003 |
| Self-pay | 1.13 | 0.239 | 0.74 to 1.71 | 0.32 | 0.5733 |
| No Charge | 1.94 | 0.752 | 0.91 to 4.15 | 2.93 | 0.0869 |
| Other | 1.34 | 0.431 | 0.72 to 2.52 | 0.86 | 0.3551 |
| Teaching Status | | | | | |
| Non-teaching* | -- | -- | -- | -- | -- |
| Teaching | 1.18 | 0.173 | 0.89 to 1.57 | 0.59 | 0.4437 |
| Urban/Rural Status | | | | | |
| Urban* | -- | -- | -- | -- | -- |
| Rural | 0.80 | 0.1869 | 0.50 to 1.26 | 1.31 | 0.2520 |
| Hospital Bed Size | | | | | |
| Small bed* | -- | -- | -- | -- | -- |
| Medium bed | 0.94 | 0.247 | 0.56 to 1.57 | 0.06 | 0.8042 |
| Large bed | 1.09 | 0.271 | 0.67 to 1.77 | 0.12 | 0.7316 |
| Hospital Ownership | | | | | |
| Government* | -- | -- | -- | -- | -- |
| Private, non-profit | 1.12 | 0.173 | 0.83 to 1.52 | 0.59 | 0.4437 |
| Private, for profit | 1.37 | 0.297 | 0.89 to 2.09 | 2.10 | 0.1476 |
| Hospital Region | | | | | |
| West* | -- | -- | -- | -- | -- |
| Northeast | 0.73 | 0.144 | 0.50 to 1.07 | 2.53 | 0.1115 |
| Midwest | 0.76 | 0.157 | 0.50 to 1.14 | 1.81 | 0.1779 |
| South | 0.97 | 0.153 | 0.71 to 1.32 | 0.03 | 0.8561 |

Odds ratios for Elixhauser comorbidities are found in Appendix C.

**Table 4.16: Additional Pairwise Comparisons for Mortality**

| | OR (SE) | 95% CI | Wald's $\chi^2$ | p-value |
|---|---|---|---|---|
| Met vs. Her | 0.55 (0.135) | 0.31 to 0.99 | 5.90 | 0.0151 |
| Met. vs. Unsp | 0.82 (0.175) | 0.49 to 1.37 | 0.86 | 0.3545 |
| Her vs. Unsp | 1.49 (0.315) | 0.90 to 2.47 | 3.62 | 0.0571 |

Met = methadone; Her = heroin; Unsp = unspecified. Adjusted $\alpha = 0.017$

*Intensity of Resource Utilization*

It was of interest to determine whether or not there was an increase in the intensity of resource utilization independent of LOS. To test this hypothesis, LOS was included as explanatory variables in the costs model. If increases in costs were not related to LOS, then this would indicate that other sources of increased costs unrelated to LOS exist. To test this in an initial step, LOS was included as an explanatory variable in the model. Even after controlling for LOS, heroin (exp(B) = 1.07, 95% CI = [1.03 to 1.12]), methadone (exp(B) = 1.10, 95% CI = [1.06 to1.15]) and unspecified opioids (exp(B) = 1.09, 95% CI = [1.06 to 1.12]) were all associated with greater costs compared to prescription opioids.

The number of procedures was also fitted to the model using a Poisson distribution and a log-link, while controlling for length of stay. Methadone and unspecified opioids were associated with a 1.24 times (95% CI = [1.12 to 1.36]) and 1.12 times (95% CI = [1.04 to 1.20]) greater number of procedures compared with prescription opioids. Methadone was also associated with a 1.14 times (95% CI = [1.02 to 1.29]) greater number of procedures compared with heroin. This seems to confirm that there are also differences in the intensity of resource utilization in terms of number of procedures performed, independent of LOS.

*Sensitivity Analyses*

*Controlling for Other Select Comorbidities*

Results from the analysis evaluating the differences in the select comorbidities are located in Appendix D, Table D.2. Univariate comparisons of costs, LOS and mortality associated with the presence of the comorbidities are displayed in Appendix D, Tables D.3 through D.5. Appendix D, Table D.6 displays the variables included for each regression model. Results from controlling for these select comorbidities are shown in Tables 4.17 through 4.19. Table 4.20 displays the adjusted coefficients for opioid type after inclusion of the additional comorbidities. Coefficients did not change substantially from the base case analyses, and were largely insensitive to the inclusion of these select comorbidities. Coefficient estimates for the additional select comorbidities are found in Appendix D, Tables D.7, D.8, and D.9.

**Table 4.17: Sensitivity Analysis for Costs, Including Other Select Comorbidities**

| Parameter | β | SE | Exp(β) (95% CI) | Z | p-value |
|---|---|---|---|---|---|
| Costs | | | | | |
| Rx Opioid* | -- | -- | -- | -- | -- |
| Heroin | 0.107 | 0.043 | 1.11 (1.02 to 1.21) | 2.51 | 0.012 |
| Methadone | 0.193 | 0.041 | 1.21 (1.12 to 1.32) | 4.68 | < 0.0001 |
| Unspecified | 0.143 | 0.024 | 1.15 (1.10 to 1.21) | 5.87 | < 0.0001 |

Only coefficient estimates for opioid type are shown here. Coefficient estimates refer to the multiplicative increase in costs for the opioid type compared to prescription opioids (RxO). This regression controls for age, race, sex, payer status, hospital rural/urban status, teaching hospital status, hospital size, hospital ownership, hospital region, area wage index (for costs), Elixhauser comorbidity indicators and the added covariates. For coefficient estimates of the added comorbidities, see Appendix D, Table D.7.

**Table 4.18: Sensitivity Analysis for LOS, Including Other Select Comorbidities**

| Parameter | β | SE | Exp(β) (95% CI) | Z | p-value |
|---|---|---|---|---|---|
| LOS | | | | | |
| Rx Opioid* | -- | -- | -- | -- | -- |
| Heroin | 0.0249 | 0.055 | 1.03 (0.92 to 1.14) | 0.46 | 0.6481 |
| Methadone | 0.1045 | 0.040 | 1.11 (1.03 to 1.20) | 2.61 | 0.009 |
| Unspecified | 0.0556 | 0.024 | 1.06 (1.01 to 1.11) | 2.28 | 0.0225 |

Only coefficient estimates for opioid type are shown here. Coefficient estimates refer to the multiplicative increase in LOS for the opioid type compared to prescription opioids (RxO). This regression controls for age, race, sex, payer status, hospital rural/urban status, teaching hospital status, hospital size, hospital ownership, hospital region, area wage index (for costs), Elixhauser comorbidity indicators and the added covariates. For coefficient estimates of the added comorbidities, see Appendix D, Table D.8.

**Table 4.19: Sensitivity Analysis for Mortality, Including Other Select Comorbidities**

| Parameter | OR | SE | 95% CI | $\chi^2$ | p-value |
|---|---|---|---|---|---|
| Opioid Type | | | | | |
| Rx Opioid* | -- | -- | -- | -- | -- |
| Heroin | 2.13 | 0.452 | 1.40 to 3.23 | 12.63 | 0.0004 |
| Methadone | 1.24 | 0.254 | 0.83 to 1.85 | 1.06 | 0.3036 |
| Unspecified | 1.49 | 0.207 | 1.14 to 1.96 | 8.32 | 0.0039 |

Only odds ratios opioid type are shown here compared to prescription opioids. This regression controls for age, race, sex, payer status, hospital rural/urban status, teaching hospital status, hospital size, hospital ownership, hospital region, and Elixhauser comorbidity indicators and the added covariates. For coefficient estimates of the added comorbidities, see Appendix D, Table D.9.

**Table 4.20 Adjusted Outcomes, Including Other Select Comorbidities**

| | Cost | LOS | Probability of Death |
|---|---|---|---|
| Heroin | 9,033 (8,316 to 9,812) | 3.5 (3.2 to 3.9) | 1.9% (1.1% to 3.2%) |
| Methadone | 9,848 (9,127 to 10,625) | 3.8 (3.6 to 4.1) | 1.1% (0.7% to 1.9%) |
| Rx Opioid | 8,117 (7,844 to 8,400) | 3.4 (3.3 to 3.6) | 0.9% (0.6% to 1.4%) |
| Unspecified | 9,367 (8,910 to 9,848) | 3.6 (3.5 to 3.8) | 1.3% (0.9% to 2.1%) |

*Sensitivity Analysis Including Median Income as a Covariate*

In the first model, median income was not included as a control variable. Because median income can be a proxy for socioeconomic status, it may be an important variable when evaluating costs as they relate to the health of the patient. As median income was missing for

various states, it was excluded in the first model to preserve the sample size. Median income by ZIP code obtained from the dataset was therefore included as a control variable. Tables 4.21 through 4.23 display coefficient estimates for opioid type and median income by ZIP code. Table 4.24 displays adjusted outcomes, when incorporating median income.

**Table 4.21: Sensitivity Analysis for Costs, Incorporating Median Income**

| Parameter | β | SE | Exp(β) (95% CI) | Z | p-value |
|---|---|---|---|---|---|
| Opioid Type | | | | | |
| Rx Opioid* | -- | -- | -- | -- | -- |
| Heroin | 0.133 | 0.042 | 1.14 (1.05 to 1.24) | 3.18 | 0.0015 |
| Methadone | 0.206 | 0.042 | 1.23 (1.13 to 1.34) | 4.85 | < 0.0001 |
| Unspecified | 0.151 | 0.025 | 1.16 (1.11 to 1.22) | 6.07 | < 0.0001 |
| Median Income | -0.016 | 0.034 | 0.98 (0.92 to 1.05) | -0.45 | 0.6525 |

Only coefficient estimates for opioid type are shown here. Coefficient estimates refer to the multiplicative increase in costs for the opioid type compared to prescription opioids. This regression controls for age, race, sex, payer status, hospital rural/urban status, teaching hospital status, hospital size, hospital ownership, hospital region, area wage index, median income, and Elixhauser comorbidity indicators.

**Table 4.22: Sensitivity Analysis for LOS, Incorporating Median Income**

| Parameter | β | SE | Exp(β) (95% CI) | Z | p-value |
|---|---|---|---|---|---|
| Opioid Type | | | | | |
| Rx Opioid* | -- | -- | -- | -- | -- |
| Heroin | 0.050 | 0.051 | 1.05 (0.95 to 1.16) | 0.97 | 0.3338 |
| Methadone | 0.096 | 0.040 | 1.10 (1.02 to 1.19) | 2.42 | 0.0156 |
| Unspecified | 0.046 | 0.025 | 1.05 (1.00 to 1.10) | 1.87 | 0.0617 |
| Median Income | -0.003 | 0.032 | 1.00 (0.94 to 1.06) | -0.1 | 0.9226 |

Only coefficient estimates for opioid type are shown here. Coefficient estimates refer to the multiplicative increase in LOS for the opioid type compared to prescription opioids. This regression controls for age, race, sex, payer status, hospital rural/urban status, teaching hospital status, hospital size, hospital ownership, hospital region, median income, and Elixhauser comorbidity indicators.

**Table 4.23: Sensitivity Analysis for Mortality, Incorporating Median Income**

| Parameter | OR | SE | 95% CI | $\chi^2$ | p-value |
|---|---|---|---|---|---|
| Opioid Type | | | | | |
| Rx Opioid* | -- | -- | -- | -- | -- |
| Heroin | 2.28 | 0.489 | 1.50 to 3.47 | 14.8 | 0.0001 |
| Methadone | 1.24 | 0.256 | 0.82 to 1.86 | 1.05 | 0.3050 |
| Unspecified | 1.52 | 0.213 | 1.16 to 2.00 | 9.11 | 0.0025 |
| Median Income | 0.81 | 0.140 | 0.58 to 1.13 | 1.51 | 0.2188 |

Only odds ratios opioid type are shown here compared to prescription opioids. This regression controls for age, race, sex, payer status, hospital rural/urban status, teaching hospital status, hospital size, hospital ownership, hospital region, median income, and Elixhauser comorbidity indicators.

**Table 4.24: Adjusted Outcomes Incorporating Median Income**

| | Cost | LOS | Probability of Death |
|---|---|---|---|
| Heroin | 9,283 (8,565 to 10,061) | 3.7 (3.3 to 4.0) | 2.1% (1.2% to 3.5%) |
| Methodone | 9,991 (9,257 to 10,784) | 3.8 (3.6 to 4.1) | 1.1% (0.7% to 1.9%) |
| Rx Opioid | 8,131 (7,844 to 8,428) | 3.5 (3.4 to 3.6) | 0.9% (0.6% to 1.4%) |
| Unspecified | 9,456 (8,985 to 9,953) | 3.6 (3.5 to 3.8) | 1.4% (0.9% to 2.1%) |

*Sensitivity Analysis using Poisoning DRGs Only*

The first model considered all visits that resulted in a primary or secondary diagnosis for opioid poisoning. However, patients may be hospitalized primarily for reasons other than poisoning, which may just act as a contributory factor in the disease process or a secondary complication unrelated to the reason for hospitalization. Because of this limitation, the original analysis was repeated using visits that resulted in DRG codes 917 and 918, which comprised 41.7% and 37.3% of all opioid poisoning visits, respectively.

After excluding non-opioid poisoning DRGs, the total number included in the sample was 10,785. After excluding suspiciously high LOS (n = 2), the total number of observations was 10,783. No observations had a missing LOS. Excluding missing charges (n = 488) and suspiciously high charges (n = 3) yielded a total of 10,294.

Mean costs and LOS were less than that than when all opioid poisoning hospitalizations were considered in the analysis. Adjusted mean costs and LOS were less than unadjusted costs. These outcomes were also less than that for when all opioid poisoning hospitalizations were included. The adjusted probability of in-hospital mortality could not be calculated due to a low number of events per included parameter (240 recorded deaths). Although the adjusted mean costs were lower than estimates obtained when considering all poisoning estimates, the coefficients did not substantially change.

**Table 4.25: Sensitivity Analysis for Costs, Excluding Non-Poisoning DRGs**

| Parameter | β | SE | Exp(β) (95% CI) | Z | p-value |
|---|---|---|---|---|---|
| Costs | | | | | |
| Opioid Type | | | | | |
| RxO* | -- | -- | -- | -- | -- |
| Heroin | 0.983 | 0.035 | 1.10 (1.03 to 1.18) | 2.80 | 0.0051 |
| Methadone | 0.191 | 0.040 | 1.21 (1.11 to 1.31) | 4.82 | < 0.0001 |
| Unspecified | 0.174 | 0.026 | 1.19 (1.13 to 1.25) | 6.82 | < 0.0001 |

Only coefficient estimates for opioid type are shown here. Coefficient estimates refer to the multiplicative increase in costs for the opioid type compared to prescription opioids. This regression controls for age, race, sex, payer status, hospital rural/urban status, teaching hospital status, hospital size, hospital ownership, hospital region, area wage index (for costs), median income, and Elixhauser comorbidity indicators.

**Table 4.26 Sensitivity Analysis for LOS, Excluding Non-Poisoning DRGs**

| Parameter | β | SE | Exp(β) (95% CI) | Z | p-value |
|---|---|---|---|---|---|
| LOS | | | | | |
| Opioid Type | | | | | |
| RxO* | -- | -- | -- | -- | -- |
| Heroin | 0.061 | 0.040 | 1.06 (0.98 to 1.15) | 1.51 | 0.1318 |
| Methadone | 0.132 | 0.036 | 1.14 (1.06 to 1.22) | 3.67 | 0.0002 |
| Unspecified | 0.095 | 0.024 | 1.10 (1.05 to 1.15) | 3.91 | < 0.0001 |

Only coefficient estimates for opioid type are shown here. Coefficient estimates refer to the multiplicative increase in LOS for the opioid type compared to prescription opioids. This regression controls for age, race, sex, payer status, hospital rural/urban status, teaching hospital status, hospital size, hospital ownership, hospital region, median income, and Elixhauser comorbidity indicators.

**Table 4.27: Adjusted Outcomes after Excluding Non-Poisoning DRGs**

| | Cost | LOS | Mortality* |
|---|---|---|---|
| Heroin | 7,638 (7,146 to 8,163 | 3.0 (2.8 to 3.3) | -- |
| Methodone | 8,376 (7,803 to 8,990) | 3.3 (3.0 to 3.5) | -- |
| Rx Opioid | 6,922 (6,680 to 7,174) | 2.8 (2.7 to 3.0) | -- |
| Unspecified | 8,236 (7,819 to 8,674) | 3.1 (3.0 to 3.3) | -- |

*Mortality model did not converge due to low number of events per parameter (240 total deaths)
Only odds ratios opioid type are shown here compared to prescription opioids. This regression controls for age, race, sex, payer status, hospital rural/urban status, teaching hospital status, hospital size, hospital ownership, hospital region, and Elixhauser comorbidity indicators.

## Section 4.3: Discussion

This study is unique in that no other studies have evaluated differences in cost between opioid types in the setting of opioid poisoning. The prevalence and incidence of prescription opioid misuse and abuse and associated poisoning have been increasing each year and is associated with significant costs to society (as observed with Specific Aim I). This helps to shed some light on various determinants of increased direct medical costs in the inpatient treatment of opioid poisoning.

Interesting differences between opioid poisoning types were found with respect to patient characteristics. Heroin patients were younger compared to those who overdosed with either prescription opioids or methadone. This confirms findings in the literature, which have shown that heroin abusers tend to be younger than those who use or even misuse/abuse prescription opioids. It may also be a reflection of the conditions for which prescription opioids are prescribed. Chronic pain may be a more common occurrence among older adults compared to younger adults.

Another interesting finding was that a larger percentage of heroin poisoning patients were male compared to either prescription opioids or methadone. This is also consistent with findings

in 2010 from the National Survey on Drug Use and Health, which reported a larger percentage of males among those reporting drug abuse.[191] Race also differed, with prescription opioids and methadone patients more likely to be white compared to heroin patients. This may reflect differences in the type of access to these medications. Prescription opioids are generally accessed through prescriptions written by physicians, although forgery and diversion are increasing problems with these agents. Some of these cases may represent improper use of these drugs used to legitimately treat pain. These reasons may be due to geography (urban vs. rural associations) or race-related differences in access to prescription opioids.

A larger percentage of heroin patients had Medicaid or "self-pay" as the primary payer. This is expected as patients who abuse heroin are likely to come from lower socioeconomic backgrounds that may qualify them for Medicaid or render them uninsured. Conversely, a larger percentage of prescription opioid patients had Medicare or private payers compared to heroin patients as their primary payers. Differences in Medicare in part reflect differences in age (greater percentage of patients over age 65) and other characteristics that may potentially qualify them for Medicare (i.e., disability). With regards to primary payer status (e.g., Medicaid, private insurance, no charge and self/pay), methadone patients interestingly appeared to be more similar to heroin poisoning patients. One possibility for this observation is that methadone can be used to treat opioid dependence, so some overlap may exist between patients dependent on heroin and those that use methadone to treat dependence. It would appear, however, that the overlap does not occur in other characteristics. In other characteristics such as age, sex, and race, methadone patients appeared more similar to those who overdose on prescription opioids. Though the reason for these differences is unclear, it can be postulated that methadone patients come from similar socioeconomic backgrounds as heroin patients, but that disparities exist with regards to

methadone as a treatment for opioid dependence. It is important to note that these findings are not conclusive, but merit further investigation into characteristics of these users.

As expected, older patients were associated with greater mean costs than younger patients. Older age was also associated with greater LOS and in-hospital mortality compared to those less than 18 years of age, especially among those greater than age 65. This is expected as older individuals are more frail and may be also be more susceptible to the effects of opioids. Differences in pharmacokinetic parameters have been demonstrated among older adults. For example, studies have shown that clearance of oxycodone is delayed with increasing age. [127, 192, 193]

Females had lower mean costs than males and were less likely to experience in-hospital mortality compared to males. However, no differences in LOS were found between males and females. Although it was not formally tested with respect to sex, this may indicate that factors other than length of stay (i.e., increased resource utilization) are responsible for the differences observed with regards to cost. The finding with mortality is consistent with other findings that have found that males are more likely to die from drug poisoning compared to females. [194] Interestingly, blacks were found to have lower costs than whites. It is not clear why this may be the case, though no differences were observed with LOS or in-hospital mortality. In 2008, it was estimated that the age-adjusted rate of drug poisoning deaths per 100,000 population was 14.7 for whites and 8.5 for blacks. [194] This can be a function of both the frequency of poisoning events and the severity of the poisonings. However, in 2010, the prevalence for substance abuse for blacks and whites was estimated to be 8.4% and 8.9%, respectively. [191] As similar differences were not found with in-hospital mortality or length of stay, the effect of race on costs is inconclusive.

Visits with a designation of "self-pay" as the primary payer were associated with lower costs and lower length of stay compared to those with private insurance. Hospitals may be pressured to reduce the length of stay for individuals without insurance to reduce the burden of costs for the patient and possibly the hospital. Case management programs at hospitals may expedite care and length of stay for the uninsured.[195] However, those with Medicaid had almost two times the odds of mortality compared to those with private insurance. It is possible that this population may experience more severe poisonings as the prevalence of drug abuse is higher among those with lower socioeconomic status.[191]

Although hospital characteristics and their effects on each of the outcomes are discussed here, it should be noted that this study was not specifically designed to evaluate the effect of these characteristics at the hospital level since the analysis was weighted at the visit level using discharge weights. Therefore, results for these characteristics are not generalizable to hospitals. Teaching status was associated with higher costs and greater LOS. The findings with respect to cost were consistent with other studies.[146, 149] The higher costs may also be reflective of greater LOS observed in this study for visits in teaching hospitals. The effect of teaching hospital status on LOS is unclear. In one regional study in Ohio, for example, it was found that risk-adjusted length of stay was lower for teaching hospitals compared to non-teaching hospitals.[196] Another study in a pediatric population found that teaching hospitals were associated with greater LOS.[197] It is possible that teaching hospitals admit more complex patients with greater severity of opioid poisoning that necessitates a longer length of stay. The models did not adjust for poisoning severity, and may be why teaching status was associated with greater LOS.

Rural hospitals were associated with lower LOS. This could be a reflection of rural hospitals handling less complex cases of opioid poisoning compared to their urban counterparts.

Urban hospitals may be located in inner-city areas where lower socioeconomic status might confer a lower health status. Furthermore, rural hospitals do not have the same breadth of services that are typically available at urban hospitals, especially for more specialized services. Complex cases may require a transfer from rural hospitals to urban hospitals where these services can be made available. This does not explain, however, why differences with costs were not observed for rural hospitals compared to urban hospitals despite the observe difference in length of stay. This is inconsistent with the findings that suggest that urban hospitals have higher administrative costs per admission than rural hospitals.[145] It is unclear why differences in costs were not observed in these categories.

Larger hospital bed size was associated with greater LOS, but was not associated with increased costs or mortality. It is unclear why there is a difference in LOS but not costs, as one would expect an increase in costs with an increase in LOS. Larger hospitals are more likely to see more complex patients than smaller hospitals, so longer lengths of stay at larger hospitals would be expected. On the other hand, larger hospitals may also be less efficient that smaller hospitals.[154-156]

Differences were observed with costs, LOS, and in-hospital mortality with each of the opioid types. As expected, methadone poisoning resulted in higher inpatient costs and LOS and poisoning by prescription opioid. Because of its longer half-life, methadone has the potential to cause prolonged symptoms of opioid poisoning. It was not, however, significantly different in costs or LOS compared with heroin. Of note, methadone was less likely to cause in-hospital mortality compared to heroin. Against expectations, heroin poisoning was associated with greater costs and mortality than prescription opioids, even after controlling for comorbidities. Although prescription opioids may have greater potencies as a whole, most prescription opioids

are ingested orally. Because heroin is most commonly injected and due to potential differences in concentrations in its street drug form, there may be a greater potential for more severe poisonings. No differences in LOS were observed comparing heroin to prescription opioids, however. Unspecified opioids were also associated with greater costs and mortality compared to prescription opioids. This is likely due to these agents being unspecified due to the lack of available history among patients with more severe presentations.

Several limitations exist with this analysis. First, beyond methadone poisoning, no further distinction was possible between other opioid analgesics. Opioid analgesics were broken down into "confirmed" prescription opioids and those that were unspecified. Unspecified opioids were separated since they can be due to heroin or other unknown opioid. This was somewhat apparent when comparing patient characteristics of those with unspecified opioids to either heroin or prescription opioids. For example, a similar percentage of visits with unspecified opioids had Medicaid listed as a primary payer as with heroin visits. On the other hand, some similarities were observed with prescription opioids with respect to race. Unspecified opioids seem to be associated with more severe poisonings than prescription opioids, as evidenced by increased costs and mortality. There is the danger of pre-selecting for less severe opioids by separating out the unspecified opioids. However, this can be justified as unspecified opioids can either be comprised of heroin or prescription opioid poisoning and separating it out can produce a cleaner analysis. These results should be interpreted with this caveat in mind. Clearer is the distinction with methadone. Methadone is quite unique in its pharmacokinetic parameters compared to other opioid types. It also plays a unique role in the treatment of opioid dependence. Evaluating the cost of treating methadone poisoning can inform policy efforts in directing interventions towards this specific patient population.

For simplicity, missing observations were excluded from the analysis. Additionally, only a total of 3.6% of visits had missing charges. Charges were more frequently missing for heroin patients than for either prescription opioids or methadone. Because of this, multiple imputation procedures would be inappropriate when comparing between opioid types because missing values can no longer be considered as missing at random, one of the core requirements for multiple imputation. If the distribution of costs for missing observations was different than those for non-missing observation, results may be biased.

To better understand the context under which the slight increase in costs occur with methadone, number of procedures was evaluated as an outcome variable while controlling for LOS along with the other factors. However, this analysis did not measure the cost of each of these procedures and essentially assumes that procedures are equal in terms of their resource utilization. Nevertheless, increases in the number of procedures are likely to increase costs. Survey design variables were not used to adjust the standard errors due to software limitations. Although survey design variables were not included the analyses, robust standard errors were applied to account for non-independence between observations at each hospital, reducing the potential for Type I error.

In conclusion, differences exist in costs, LOS and in-hospital mortality depending on opioid type. Heroin is associated with greater costs and mortality compared to specified prescription opioids. Methadone is associated with greater costs and LOS than specified prescription opioids. Unspecified opioids were associated with greater costs than specified prescription opioids, but were not found to be different from methadone or heroin in any other pairwise comparison.

# Chapter V:

## Methods, Results and Discussion for Specific Aim III:

Evaluation of Opioids as Determinants of Hospitalization and Hospitalization Type Among Opioid-Related ED Visits

### Section 5.1: Methods

*Database*

The Drug Abuse Warning Network (DAWN) database from 2009 was used for this specific aim. DAWN is a public health surveillance system administered by the Substance Abuse and Mental Health Services Administration (SAMHSA) that monitors drug-related visits to emergency departments.[160] The target sample for DAWN hospitals are non-Federal, short-stay, general medical and surgical hospitals across the United States that have at least one 24-hour ED.[160] Hospitals are sampled using a multistage sampling design from twelve metropolitan statistical areas that can be weighted to produce national estimates of drug-related ED visits. Data were collected directly from the medical records of patients treated in the ED by trained DAWN reporters using a standardized case report form. Data collected on the form include the facility number, date of visit, time of visit, age, home ZIP code, sex, race/ethnicity, case description, case type, diagnoses, case dispositions, involved substances (up to 22), route of administration, toxicology confirmations, and other general comments.[160] Although all of these data are collected, diagnoses, comments, and specific case descriptions are not included in available datasets.

DAWN visits did not include those where there was no evidence of recent drug use, if the patient left the ED without being treated, consumed a nonpharmaceutical substance but did not inhale it, history of drug use without recent use, alcohol only among those age 21 years or older, if drugs were mentioned in the ED record or identified in the toxicology reports but were not related to the ED visits, and if the patient was treated due to undermedication.[160]

DAWN reporters assign each case to one of eight case types. These case types are assigned based an algorithm using a "DAWN Decision Tree", depicted in Appendix E. Of note, most cases of drug abuse fall in the "other" category due to lack of explicit documentation of substance abuse.[160] Furthermore, descriptions of symptoms are not provided, rendering the categorization of opioid poisoning difficult.

Disposition includes three broad categories: treated and released (T&R), admitted to same hospital, or other disposition. T&R visits can be categorized into three subcategories: discharged home, released to police/jail, or referred to detoxification/treatment. Same-hospital admissions can be categorized into those admitted to intensive or critical care units (hereby referred to as ICU), surgery, chemical dependency/detoxification unit, psychiatric unit, or other inpatient units. Psychiatric and chemical dependency units were combined into one category in the available dataset. Dispositions classified as "other" include those who were transferred, left against medical advice, died, "other disposition", or not documented.

*Sample Selection*

Drugs are coded in DAWN using a modified version of the Multum *Lexicon*, © 2011 (Multum Information Services Inc.). Because this coding system only categorizes legal drugs, it was modified in the DAWN dataset to include illegal drugs and other substances not typically included in the Multum database. Opioids that were considered were based on the frequency of

their appearance in the dataset. A category called "collapsed" was created for low-frequency opioids. These included opiums, meperidine, oymorphone, and butorphanol.

As it is of interest to evaluate ED visits that are likely to be poisoning-related, it is important to carefully select the types of cases that are included in the final sample. Unlike in Specific Aim I, it was decided to apply more liberal inclusion criteria for the visits. Case types classified as "seeking detoxification" were excluded since these cases are unlikely to have presented with symptoms of poisoning. However, T&R visits that resulted in a referral for detoxification or dependency treatment were retained in the denominator as it is still possible that these cases may represent poisoning events after applying the exclusion criterion for case type "seeking detoxification". Visits were also excluded from the analysis if the disposition was missing or undocumented or if the patient died after entering the ED but before being discharged or admitted. For the purposes of the analysis, "transfers" were considered as admissions.

*Statistical Analysis*

Unweighted and weighted demographic and patient characteristics were described and reported. These included age, sex, race, and case type. Pearson's $\chi^2$ test was used to compare the proportions of admissions within each subcategory for the unweighted analysis. In the weighted analysis, the Rao-Scott $\chi^2$ test was used to account for the complex survey design. Unweighted and weighted estimates for each of the opioid types were reported for all visits and proportions of admitted patients for each opioid type were reported. Unadjusted logistic regression was used to evaluate the likelihood of admission for each opioid, compared to all other opioids. Adjusted logistic regression was used to evaluate the likelihood of admission for each opioid, after adjusting for patient characteristics such as age, sex, race, and case type. Age category "< 18" was chosen as the reference group to show possible trends in coefficient

estimates with increasing age. Whites were chosen as the comparison group for race as this group represented the most frequently occurring race. The "other" category was chosen as the reference category for case type of most cases of "other" are abuse-related. This made it possible to make the best comparison between abuse-related visits and other types of visits such as overmedication and suicide attempts.

Unweighted and weighted estimates of each opioid type were estimated by admission type among all visits that resulted in a same-hospital admission or transfer. The categories that were evaluated included ICU admissions, surgery, psychiatric/detoxification admissions, "other" admissions, and transfers. Unadjusted and adjusted multinomial logistic regression were performed on opioids using "other" admissions as the referent category for the dependent variable. By exclusion, "other" admissions are likely to consist of other general types of admission. Surgery was excluded from the multinomial logistic regression due to small cell sizes. Because each opioid was entered in separately, the referent category for each opioid was all other opioids (i.e., heroin vs. all other non-heroin opioids).

SAS 9.3 was used to conduct the analyses. PROC SURVEYFREQ and PROC SURVEYLOGISTIC were used to conduct the weighted frequency estimates along with the binomial and multinomial logistic regression. An $\alpha$ of 0.05 was used to assess significant of the variables that were tested.

## Section 5.2: Results

*Patient Characteristics*

Unweighted and weighted estimates for patient characteristics and the percentages for each that are admitted are found in Table 5.1 and 5.2. A total of 66,296 visits met the inclusion and exclusion criteria, representing a weighted sum of 795,898 for the sample. The largest group comprised individuals aged 34 to 54 years (44.1%), followed by those aged 18 to 34 years (33.1%), 55 to 64 years (11.7%), greater than 65 years (8.7%) and less than 18 years of age (2.5%). There were more males than females in the sample (53.5% vs. 46.5%). Whites were the most frequently occurring group (55.8%), followed by blacks (17.4%), Hispanics/Latinos (11.2%) and other (1.5%). A significant percent of observations did not have a documentation of race (14.1%). The most frequently occurring case type was for the "other" category (61.6%). Adverse reaction, overmedication, and suicide attempt were the next three most commonly occurring case types (21.7%, 12.0% and 4.1%, respectively). The least commonly occurring case types were for accidental ingestion and malicious poisoning (0.5% and 0.1%, respectively).

Significant differences were found with respect to age, race, and case type in both the weighted and unweighted analyses. Differences in weighted estimates are discussed here. The most frequently admitted group was those aged 65 years and older (37.3%) while the least frequently admitted group was those between the ages of 18 and 34 years (26.7%). Whites, blacks and "other" races had the highest admission rates (32.5%, 33.2%, and 32.0%, respectively) while those identified as Hispanic/Latino or undocumented races had lower admission rates (20.8% and 29.7%, respectively). The most frequently admitted case type was for those cases classified as suicide attempt (78.0%), followed by overmedication (48.6%),

"other" (28.9%), accidental ingestion (22.8%), and adverse reaction (21.6%). Weighted estimates for malicious poisoning were unable to be estimated due to small unweighted cell sizes for that subgroup.

**Table 5.1: Unweighted Patient Characteristics for Opioid-Related ED Visits**

| | Total (% of sample)* | Admitted (% in group)* | p-value |
|---|---|---|---|
| Age Category | | | |
| < 18 | 1,625 (2.5) | 513 (31.6) | < 0.0001 |
| 18 to 34 | 21,956 (33.1) | 6,185 (28.2) | ($\chi^2_{df=4}$ = 869.32) |
| 34 to 54 | 29,224 (44.1) | 10,006 (34.2) | |
| 55 to 64 | 7,734 (11.7) | 3,078 (39.8) | |
| > 65 | 5,736 (8.7) | 2,681 (46.7) | |
| Sex | | | |
| Male | 35,464 (53.5) | 12,099 (34.1) | 0.1851 |
| Female | 30,802 (46.5) | 10,358 (33.6) | ($\chi^2_{df=1}$ = 1.76) |
| Race | | | |
| White | 36,966 (55.8) | 12,768 (34.5) | < 0.0001 |
| Black | 11,557 (17.4) | 3,978 (34.4) | ($\chi^2_{df=4}$ = 116.14) |
| Hispanic/Latino | 7,437 (11.2) | 2,137 (28.7) | |
| Other | 1,020 (1.5) | 296 (29.0) | |
| Undocumented | 9,316 (14.1) | 3,292 (35.3) | |
| Case Type | | | |
| Suicide attempt | 2,692 (4.1) | 2,065 (76.7) | < 0.0001 |
| Adverse reaction | 14,393 (21.7) | 3,448 (24.0) | ($\chi^2_{df=5}$ = 3,917.24) |
| Overmedication | 7,945 (12.0) | 4,000 (50.4) | |
| Malicious poisoning | 65 (0.1) | 13 (20.0) | |
| Accidental ingestion | 346 (0.5) | 95 (27.5) | |
| Other | 40,855 (61.6) | 12,850 (31.5) | |

*% of sample represents the unweighted percent of the sample that have the particular characteristic (e.g., 2.5% of the entire sample are less than age 18). % in group represents the unweighted percent within each subgroup (e.g., percent admitted within age category less than 18)..

**Table 5.2: Weighted Patient Characteristics for Opioid-Related ED Visits***

| | Total (% of sample) | Admitted (% in group) | p-value |
|---|---|---|---|
| Age Category | | | |
| < 18 | 27,159 (3.4) | 7,764 (28.6) | < 0.0001 |
| 18 to 34 | 286,215 (36.0) | 76,504 (26.7) | ($\chi^2_{df=4}$ = 28.28 |
| 34 to 54 | 296,533 (37.3) | 99,514 (33.6) | |
| 55 to 64 | 89,972 (11.3) | 30,040 (33.4) | |
| > 65 | 95,955 (12.1) | 35,797 (37.3) | |
| Sex | | | 0.1583 |
| Male | 399,161 (50.2) | 128,661 (32.2) | ($\chi^2_{df=1}$ = 1.99) |
| Female | 396,640 (49.8) | 120,940 (30.5) | |
| Race | | | |
| White | 573,232 (72.0) | 186,386 (32.5) | 0.0008 |
| Black | 79,950 (10.0) | 26,538 (33.2) | ($\chi^2_{df=4}$ = 19.08) |
| Hispanic/Latino | 66,551 (8.4) | 13,914 (20.9) | |
| Other | 8,574 (1.1) | 2,741 (32.0) | |
| Undocumented | 67,591 (8.5) | 20,078 (29.7) | |
| Case Type | | | |
| Suicide attempt | 34,389 (4.3) | 26,813 (78.0) | |
| Adverse reaction | 221,847 (27.9) | 47,980 (21.6) | < 0.0001 |
| Overmedication | 100,520 (12.6) | 48,815 (48.6) | ($\chi^2_{df=5}$ = 249.17) |
| Malicious poisoning | 1,018 (0.1) | ** | |
| Accidental ingestion | 6,367 (0.8) | 1,449 (22.8) | |
| Other | 431,758 (54.2) | 124,565 (28.9) | |

*Numbers may not add up to the total due to missing values
** Estimates were unable to be computed due to a low unweighted cell size.

*Frequencies for Opioids*

Tables 5.3 and 5.4 provide unweighted and weighted estimates of opioids and the percent admitted for each type. The most frequently reported opioid was for heroin (31.9%), followed by oxycodone (19.7%), hydrocodone (18.2%) and methadone (11.5%). After weighting the sample, however, oxycodone was the most frequently reported (27.5%), followed by hydrocodone (22.4%), heroin (18.8%), and methadone (9.3%). Patients with documented morphine use had the highest weighted proportion of patients admitted (39.4%), while the lowest was for codeine (23.8%).

**Table 5.3: Unweighted Frequencies for Opioids in Sample**

| | Total n (% of sample) | Admitted n (% within group) |
|---|---|---|
| Heroin | 21,124 (31.9) | 7,236 (34.3) |
| Hydrocodone | 12,066 (18.2) | 4,023 (33.3) |
| Oxycodone | 13,068 (19.7) | 4,278 (32.7) |
| Methadone | 7,623 (11.5) | 2,352 (30.9) |
| Morphine | 3,166 (4.8) | 1,310 (41.4) |
| Hydromorphone | 1,832 (2.8) | 633 (34.5) |
| Fentanyl | 1,852 (2.8) | 765 (41.3) |
| Codeine | 2,297 (3.5) | 648 (28.2) |
| Buprenorphine | 1,200 (1.8) | 290 (24.2) |
| Propoxyphene | 1,133 (1.7) | 462 (40.8) |
| Opioid, NOS | 7,648 (11.5) | 3,113 (40.7) |
| Collapsed | 320 (0.5) | 100 (31.3) |
| All | 66,296 (100.0) | 22,471 (31.4) |

**Table 5.4: Weighted Frequencies for Opioids**

| | Total n (% of sample) | Admitted n (% within group) |
|---|---|---|
| Heroin | 149,836 (18.8) | 45,005 (30.0) |
| Hydrocodone | 178,488 (22.4) | 54,608 (30.6) |
| Oxycodone | 218,803 (27.5) | 69,782 (31.9) |
| Methadone | 73,860 (9.3) | 25,122 (34.0) |
| Morphine | 49,368 (6.2) | 19,462 (39.4) |
| Hydromorphone | 25,171 (3.2) | 7,536 (29.9) |
| Fentanyl | 34,679 (4.4) | 12,700 (36.6) |
| Codeine | 29,051 (3.7) | 6,914 (23.8) |
| Buprenorphine | 18,424 (2.3) | 4,763 (25.9) |
| Propoxyphene | 23,109 (2.9) | 7,935 (34.3) |
| Opioid, NOS | 92,084 (11.5) | 34,361 (37.3) |
| Collapsed | 6,998 (0.9) | 2,024 (29.9) |
| All | 795,898 (100.0) | 249,656 (31.4) |

*Determinants of Hospitalization*

In the unadjusted logistic regression, only visits with hydrocodone, methadone, morphine, fentanyl and unspecified opioids were shown to be significantly associated with admission to the hospital. Odds ratios and associated 95% confidence intervals for each of the opioids are provided in Table 5.5. Hydrocodone was associated with 1.3 times (95% CI = 1.0 to

1.6) greater odds of admission compared to other opioids. Methadone and fentanyl visits had a 1.4 times (95% CI = [1.0 to 1.9]) and 1.6 times (95% CI = [1.0 to 2.4]) greater odds of admission compared to other opioids, respectively. Visits involving unspecified opioids were associated with 1.8 times (95% CI = [1.3 to 2.4]) greater odds in hospitalization compared to other opioids.

Table 5.6 displays results of the adjusted logistic regression. After adjusting for age, sex, race and case type, heroin, methadone, morphine, and unspecified opioids were observed to be associated with hospital admission. Visits involving heroin had 1.5 times (95% CI = [1.1 to 2.1]) times greater odds of hospital admission compared to other opioids. Visits involving methadone had 1.4 times (95% CI = [1.0 to 1.9]) greater odds in hospitalization and visits with morphine had 1.7 times (95% CI = [1.2 to 2.5]) times greater odds hospital admission compared to other opioids. Visits involving unspecified opioids had 1.9 times (95% CI = [1.5 to 2.5]) greater odds of hospital admission compared to other opioids. After adjusting for other patient characteristics, fentanyl was no longer significantly associated with admission. Compared to those less than 18 years of age, those aged 18 to 34 years had 29% (95% CI = [8% to 45%]) lower odds of admission. Conversely, those greater than age 65 had 1.9 (95% CI = [1.5 to 2.4]) times greater odds of admission compared to those less than 18 years of age. Males had 1.1 times (95% CI = [1.0 to 1.3]) greater odds of admission compared to females. Compared to whites, those of Hispanic or Latino descent had 49% (95% CI = [29% to 64%]) lower odds of admission. Compared to those in the "other" case type category, suicide attempts were associated with a 10.8 (95% CI = [6.0 to 19.3]) times greater odds of admission. Cases of overmedication were associated with a 2.4 times (95% CI = [2.0 to 2.8]) greater odds of admission. Visits for adverse reactions had 38% (95% CI = [26% to 49%] lower odds of admission.

**Table 5.5 Unadjusted Logistic Regression for Hospitalization**

| | OR | 95% CI | Wald's $\chi^2$ | p-value |
|---|---|---|---|---|
| Heroin | 1.28 | 0.93 to 1.76 | 2.25 | 0.1335 |
| Hydrocodone | 1.28 | 1.03 to 1.60 | 4.75 | 0.0293 |
| Oxycodone | 1.31 | 0.95 to 1.79 | 2.73 | 0.0986 |
| Methadone | 1.40 | 1.04 to 1.89 | 5.04 | 0.0248 |
| Morphine | 1.80 | 1.29 to 2.51 | 11.82 | 0.0006 |
| Hydromorphone | 1.15 | 0.93 to 1.44 | 1.65 | 0.1993 |
| Fentanyl | 1.58 | 1.03 to 2.43 | 4.35 | 0.0371 |
| Codeine | 0.92 | 0.67 to 1.27 | 0.25 | 0.6176 |
| Buprenorphine | 0.97 | 0.74 to 1.26 | 0.06 | 0.8021 |
| Propoxyphene | 1.48 | 0.65 to 1.88 | 3.21 | 0.0730 |
| Opioid, NOS | 1.77 | 1.30 to 2.41 | 13.10 | 0.0003 |
| Collapsed | 1.10 | 0.65 to 1.88 | 0.13 | 0.7204 |

**Table 5.6: Adjusted Logistic Regression for Hospitalization**

| | OR | 95% CI | Wald's $\chi^2$ | p-value |
|---|---|---|---|---|
| Age Category | | | | |
| < 18* | -- | -- | -- | -- |
| 18 to 34 | 0.71 | 0.55 to 0.92 | 46.84 | < 0.0001 |
| 34 to 54 | 0.99 | 0.74 to 1.32 | 1.57 | 0.2105 |
| 55 to 64 | 1.10 | 0.82 to 1.48 | 0.12 | 0.7301 |
| > 65 | 1.85 | 1.45 to 2.37 | 57.01 | < 0.0001 |
| Sex | | | | |
| Female* | -- | -- | -- | -- |
| Male | 1.14 | 1.04 to 1.26 | 7.30 | 0.0069 |
| Race | | | | |
| White* | -- | -- | -- | -- |
| Black | 1.04 | 0.79 to 1.37 | 2.36 | 0.1244 |
| Hispanic/Latino | 0.51 | 0.36 to 0.71 | 21.5 | < 0.0001 |
| Other | 1.04 | 0.69 to 1.56 | 1.18 | 0.2775 |
| Undocumented | 0.92 | 0.68 to 1.25 | 0.12 | 0.6365 |
| Case Type | | | | |
| Other* | -- | -- | -- | -- |
| Suicide attempt | 10.81 | 6.04 to 19.32 | 64.42 | < 0.0001 |
| Adverse reaction | 0.62 | 0.51 to 0.74 | 25.32 | < 0.0001 |
| Overmedication | 2.37 | 2.02 to 2.77 | 112.77 | < 0.0001 |
| Accidental ingestion | 0.81 | 0.44 to 1.46 | 0.50 | 0.4794 |
| Malicious poisoning | 0.09 | 0.03 to 0.25 | 21.46 | < 0.0001 |
| Heroin | 1.54 | 1.14 to 2.09 | 7.84 | 0.0051 |
| Hydrocodone | 1.13 | 0.90 to 1.42 | 1.05 | 0.3051 |
| Oxycodone | 1.24 | 0.89 to 1.69 | 1.70 | 0.1918 |
| Methadone | 1.41 | 1.03 to 1.93 | 4.50 | 0.0339 |
| Morphine | 1.73 | 1.18 to 2.53 | 7.87 | 0.0050 |
| Hydromorphone | 1.22 | 0.97 to 1.54 | 2.76 | 0.0968 |
| Fentanyl | 1.47 | 0.87 to 2.48 | 0.38 | 0.1499 |
| Codeine | 0.94 | 0.67 to 1.32 | 0.13 | 0.7179 |
| Buprenorphine | 1.10 | 0.87 to 1.39 | 0.70 | 0.4025 |
| Propoxyphene | 1.38 | 0.86 to 2.21 | 1.76 | 0.1840 |
| Opioid, NOS | 1.92 | 1.47 to 2.49 | 23.36 | < 0.0001 |
| Collapsed | 1.16 | 0.69 to 1.97 | 0.32 | 0.5738 |

*Referent category

**Table 5.7: Unweighted Frequencies of Admission Type by Opioid**

| | ICU | Surgery | Psychiatry/Detox | Other Admit | Transfer |
|---|---|---|---|---|---|
| Heroin (n = 7,236) | 508 (7.0) | 241 (3.3) | 1,604 (22.2) | 3,549 (49.1) | 1,334 (18.4) |
| Hydrocodone (n = 4,023) | 593 (14.7) | 36 (0.9) | 575 (14.3) | 2,153 (53.5) | 666 (16.6) |
| Oxycodone (n = 4,278) | 618 (14.5) | 20 (0.5) | 505 (11.8) | 2,426 (56.7) | 709 (16.6) |
| Methadone (n = 2,352) | 380 (16.2) | 18 (0.8) | 339 (14.4) | 1,333 (56.7) | 282 (12.0) |
| Morphine (n = 1,310) | 245 (18.7) | 19 (1.5) | 76 (5.8) | 838 (64.0) | 132 (10.1) |
| Hydromorphone (n = 633) | 90 (14.2) | 7 (1.1) | 35 (5.5) | 443 (70.0) | 58 (9.2) |
| Fentanyl (n = 765) | 135 (17.7) | 6 (0.8) | 33 (4.3) | 535 (69.9) | 56 (7.3) |
| Codeine (n = 648) | 88 (13.6) | 8 (1.2) | 64 (9.9) | 374 (57.7) | 114 (17.6) |
| Buprenorphine (n = 290) | 26 (9.0) | 1 (0.3) | 51 (17.6) | 128 (44.1) | 84 (29.0) |
| Propoxyphene (n = 462) | 85 (18.4) | 3 (0.7) | 51 (11.0) | 252 (54.6) | 71 (15.4) |
| Opioid, NOS (n = 3,113) | 452 (14.5) | 28 (0.9) | 592 (19.0) | 1,523 (48.9) | 518 (16.6) |
| Collapsed (n = 100) | 16 (16.0) | 0 (0.0) | 11 (11.0) | 57 (57.0) | 16 (16.0) |
| All (n = 22,471) | 2,796 (12.4) | 368 (1.6) | 3,529 (15.7) | 12,184 (54.2) | 3,594 (16.0) |

**Table 5.8: Weighted Frequencies of Admission Type by Opioid**

| | ICU | Surgery | Psychiatry/Detox | Other Admit | Transfer |
|---|---|---|---|---|---|
| Heroin (n = 45,005) | 4,625 (10.3) | 665 (1.5) | 8,305 (18.5) | 18,651 (41.4) | 12,759 (28.4) |
| Hydrocodone (n = 54,608) | 14,148 (25.9) | 1,406 (2.6) | 3,860 (7.1) | 26,349 (48.3) | 8,846 (16.2) |
| Oxycodone (n =69,782) | 17,384 (24.9) | * | 4,132 (5.9) | 32,378 (46.4) | 15,733 (22.5) |
| Methadone (n = 22,471) | 7,142 (28.4) | * | 1,618 (6.4) | 10,920 (43.5) | 4,981 (3.6) |
| Morphine (n = 19,462) | 5,705 (19.3) | * | 363 (1.9) | 9,448 (48.5) | 3,447 (17.7) |
| Hydromorphone (n = 7,536) | 1,191 (15.8) | * | 232 (3.1) | 5,050 (67.0) | 849 (11.3) |
| Fentanyl (n = 12,700) | 3,418 (26.9) | * | 689 (5.4) | 7,420 (28.4) | 1,060 (8.3) |
| Codeine (n = 6,914) | 1,304 (18.9) | * | 148 (2.1) | 4,061 (58.7) | 1,133 (3.8) |
| Buprenorphine (n = 4,763) | * | * | 431 (9.1) | 1,524 (32.0) | 1,896 (39.8) |
| Propoxyphene (n = 7,935) | 2,085 (26.3) | * | 303 (3.8) | 3,943 (49.7) | 1,596 (20.1) |
| Opioid, NOS | 8,747 (15.5) | * | 3,176 (9.2) | 14,610 (42.5) | 7,758 (22.6) |
| Collapsed (n = 2,024) | * | * | * | 658 (32.5) | * |
| All (n = 249,656) | 54,287 (21.7) | 3,505 (1.4) | 20,859 (8.4) | 119,647 (47.9) | 51,358 (3.9) |

*Weighted estimates not provided due to low unweighted sample sizes.

*Frequencies for Hospitalization Type*

Unweighted and weighted cell counts by opioid and admission type for admitted patients are provided in Tables 5.7 and 5.8. The most common admission category for all opioid admissions was for "other" admissions (47.9%), followed by ICU admissions (21.7%), psychiatric/detoxification admissions (8.4%), transfers (3.9%) and surgery (1.4%). The highest proportion for ICU admissions among all admissions was observed for methadone, hydrocodone, oxycodone and fentanyl (28.4%, 25.9%, 24.9% and 26.9%, respectively). The lowest proportion of ICU admissions was observed for unspecified opioids, hydromorphone, codeine, and morphine (15.5%, 15.8%, 18.9%, and 19.3%, respectively). Psychiatric or detoxification admissions were highest for morphine (18.5% vs. 9.1% or less for other categories). The lowest proportion of psychiatric admissions was observed for morphine and codeine (1.9% and 2.1%, respectively). Highest proportions for "other" admissions were observed for hydromorphone and codeine (67.0% and 58.7%, respectively) while the lowest were for "other" opioids and buprenorphine (32.5% and 32.0%, respectively). Transfers were greatest for buprenorphine (39.8%). This was followed by heroin (28.4%), oxycodone (22.5%), and propoxyphene (20.1%). The lowest percentages of transfers were found for methadone (3.6%) and codeine (3.8%).

*Determinants of Hospitalization Type among Admitted Patients*

Results for the unadjusted multinomial logistic regression are in Table 5.9. The odds ratios refer to the odds of being admitted into a particular unit instead of being admitted to "other" (i.e., non-psychiatric, non-ICU, non-transfers) units for a particular opioid when compared to all other opioids. Heroin was associated with a 4.45 (95% CI = [2.71 to 7.31]) times greater odds of admission to a psychiatric or detoxification unit and 2.80 (95% CI = [1.57

to 4.99]) times greater odds of transfer instead of being admitted to "other" units, when compared to all other opioids. Patients with documented hydrocodone, methadone, and morphine use had 2.04 (95% CI = [1.45 to 2.88]), 2.23 (95% CI = [1.29 to 3.84]), and 2.03 (95% CI = [1.45 to 2.84]) times greater odds of admission to the ICU instead of "other" units, respectively. Patients with in the ED due to morphine, hydromorphone, and codeine use had 64% (95% CI = [13% to 85%]), 60% (95% CI = [18% to 80%]) and 65% (95% CI = [19% to 85%]) lower odds of admission to psychiatric or detoxification units instead of other units when compared to all other opioids. Patients in the ED due to buprenorphine had 2.35 (95% CI = [1.09 to 5.05]) times greater odds of hospitalization in a psychiatric or detoxification unit instead of "other" units, compared to all other opioids. Visits in which opioids were unable to be identified had 2.36 (95% CI = [1.24 to 4.47]) and 2.11 (95% CI = [1.15 to 3.86]) times greater odds of hospitalization in the ICU or transferred instead of being admitted in "other" units compared to all else.

After adjusting for age, sex, race, and case type, fewer significant associations were observed with specific opioids (Table 5.10). Heroin patients had 2.20 (95% CI = [1.37 to 3.54]) times greater odds of hospitalization in a psychiatric or detoxification unit instead of "other" units compared to all other opioids. Compared with all other opioids, hydrocodone, methadone, morphine and fentanyl patients had 1.67 (95% CI = [1.09 to 2.55]), 1.84 (95% CI = [1.10 to 3.09]), 2.32 (95% CI = [1.63 to 3.32], and 2.12 (95% CI = [1.22 to 3.68]) times greater odds of hospitalization in the ICU instead of "other" units, respectively. Oxycodone and morphine patients were associated with a 1.54 (95% CI = [1.03 to 2.31]) and 1.71 (95% CI = [1.19 to 2.45]) times greater odds of transfer than hospitalization in "other" units compared to all other opioids. Compared to all other opioids, codeine patients had 67% (95% CI = [14% to 87%])

lower odds of admission to a psychiatric or detoxification unit instead of "other" units. Finally, patients with unidentified opioid had 1.97 (95% CI = [1.21 to 3.19]) times greater odds of hospitalization in the ICU instead of "other" units compared to all other opioids.

Older age was associated with a decreased odds of being hospitalized in the ICU instead of "other" units. This association was significant for those aged 34 to 54 years (OR = 0.43, 95% CI = [0.21 to 0.88]), 55 to 64 years (OR = 0.35, 95% CI = [0.16 to 0.74]), and greater than 65 years (OR = 0.27, 95% CI = [0.13 to 0.56) when compared to those less than 18 years of age. Similar patterns were noted for transfers, with decreasing odds of transfer with greater age (see Table 5.10). Greater age was also associated with a decreased odds of psychiatric or detoxification admissions when comparing those aged 55 to 64 years (OR = 0.31, 95% CI = [0.12 to 0.77]) and those greater than 65 years of age (OR =0.07, 95% CI = [0.02 to 0.28]) to those less than 18 years of age.

No significant associations were observed for sex. Compared to whites, blacks had 46% (95% CI = [2% to 71%]) lower odds of transfer instead of admission to "other" units. No other significant associations were observed for race. Compared to case types classified as "other", suicide attempt cases were significantly associated with greater odds of an ICU admission (OR = 3.06, 95% CI = [1.65 to 5.67]), psychiatric/detoxification admission (OR = 2.81, 95% CI = [1.35 to 5.86]) or a transfer (OR = 3.13, 95% CI = [2.07 to 4.74]) instead of hospitalization in "other" units. Conversely, cases classified as "adverse reactions" were associated with lower of admission into these three categories (OR = 0.39, 95% CI = [0.22 to 0.69]; OR = 0.07, 95% CI = [0.03 to 0.14]; OR = 0.19 (95% CI = [0.11 to 0.34]).

**Table 5.9: Unadjusted Multinomial Logistic Regression for Hospitalization Type**

| | OR (Reference = "Other Admission") | | |
|---|---|---|---|
| | ICU | Psychiatry/Detox | Transfer |
| Heroin | 0.98 (0.68 to 1.43) | 4.45 (2.71 to 7.31) | 2.80 (1.57 to 4.99) |
| Hydrocodone | 2.04 (1.45 to 2.88) | 1.48 (0.80 to 2.76) | 1.32 (0.90 to 1.95) |
| Oxycodone | 1.88 (0.78 to 4.56) | 1.21 (0.74 to 1.96) | 1.91 (1.20 to 3.04) |
| Methadone | 2.23 (1.29 to 3.84) | 1.23 (0.51 to 2.95) | 1.55 (0.94 to 2.53) |
| Morphine | 2.03 (1.45 to 2.84) | 0.36 (0.15 to 0.87) | 1.34 (0.86 to 2.09) |
| Hydromorphone | 0.72 (0.39 to 1.33) | 0.40 (0.20 to 0.82) | 0.57 (0.30 to 1.17) |
| Fentanyl | 1.42 (0.87 to 2.31) | 0.90 (0.36 to 2.23) | 0.47 (0.19 to 1.18) |
| Codeine | 1.16 (0.69 to 1.97) | 0.35 (0.15 to 0.81) | 1.12 (0.63 to 2.00) |
| Buprenorphine | 2.03 (0.93 to 4.42) | 2.35 (1.09 to 5.05) | 4.36 (1.51 to 12.64) |
| Propoxyphene | 1.80 (0.83 to 3.89) | 0.73 (0.24 to 2.20) | 1.53 (0.99 to 2.37) |
| Opioid, NOS | 2.36 (1.24 to 4.47) | 2.12 (0.98 to 4.59) | 2.11 (1.15 to 3.86 |
| Collapsed | 2.95 (0.60 to 14.45) | 3.62 (0.41 to 32.4) | 3.0 (0.89 to 10.1) |

**Table 5.10: Adjusted Multinomial Logistic Regression for Hospitalization Type**

| | OR (Reference = "Other Admission") | | |
|---|---|---|---|
| | ICU | Psychiatry/Detox | Transfer |
| Age Category | | | |
| < 18 | -- | -- | -- |
| 18 to 34 | 0.43 (0.17 to 1.08) | 0.68 (0.24 to 1.93) | 0.37 (0.11 to 1.31) |
| 34 to 54 | 0.43 (0.21 to 0.88) | 0.55 (0.23 to 1.32) | 0.27 (0.09 to 0.82) |
| 55 to 64 | 0.35 (0.16 to 0.74) | 0.31 (0.12 to 0.77) | 0.12 (0.04 to 0.33) |
| > 65 | 0.27 (0.13 to 0.56) | 0.07 (0.02 to 0.28) | 0.11 (0.03 to 0.43) |
| Sex | | | |
| Female | -- | -- | -- |
| Male | 1.17 (0.89 to 1.54) | 0.82 (0.59 to 1.14) | 1.02 (0.78 to 1.34) |
| Race | | | |
| White | -- | -- | -- |
| Black | 0.62 (0.33 to 1.16) | 1.15 (0.70 to 1.91) | 0.54 (0.29 to 0.98) |
| Hispanic/Latino | 0.67 (0.35 to 1.30) | 1.21 (0.57 to 2.57) | 0.89 (0.35 to 2.22) |
| Other | 0.63 (0.18 to 2.15) | 0.68 (0.18 to 2.50) | 1.18 (0.48 to 2.91) |
| Undocumented | 0.83 (0.40 to 1.74) | 1.44 (0.77 to 2.70) | 0.37 (0.15 to 0.95) |
| Case Type | | | |
| Other | -- | -- | -- |
| Suicide attempt | 3.06 (1.65 to 5.67) | 2.81 (1.35 to 5.86) | 3.13 (2.07 to 4.74) |
| Adverse reaction | 0.39 (0.22 to 0.69) | 0.07 (0.03 to 0.14) | 0.19 (0.11 to 0.34) |
| Overmedication | 1.45 (0.90 to 2.34) | 0.68 (0.44 to 1.06) | 0.68 (0.44 to 1.06) |
| Malicious poisoning | 0.46 (0.09 to 2.46) | 0.52 (0.06 to 4.54) | 0.60 (0.11 to 3.30) |
| Accidental ingestion | 0.21 (0.03 to 1.58) | ** | 1.18 (0.34 to 4.07) |
| Heroin | 0.82 (0.57 to 1.17) | 2.20 (1.37 to 3.54) | 1.62 (0.90 to 2.93) |
| Hydrocodone | 1.67 (1.09 to 2.55) | 1.25 (0.60 to 2.61) | 1.06 (0.63 to 1.79) |
| Oxycodone | 1.65 (0.72 to 3.77) | 1.09 (0.70 to 1.70) | 1.54 (1.03 to 2.31) |
| Methadone | 1.84 (1.10 to 3.09) | 0.97 (0.46 to 2.04) | 1.17 (0.69 to 1.98) |
| Morphine | 2.32 (1.63 to 3.32) | 0.50 (0.20 to 1.24) | 1.71 (1.19 to 2.45) |
| Hydromorphone | 0.83 (0.43 to 1.62) | 0.53 (0.24 to 1.15) | 0.73 (0.37 to 1.14) |
| Fentanyl | 2.12 (1.22 to 3.68) | 2.06 (0.81 to 5.25) | 0.88 (0.35 to 2.17) |
| Codeine | 1.09 (0.58 to 2.04) | 0.33 (0.13 to 0.86) | 1.11 (0.58 to 2.15) |
| Buprenorphine | 1.54 (0.64 to 3.71) | 1.79 (0.87 to 3.70) | 2.33 (0.75 to 7.25) |
| Propoxyphene | 1.81 (0.72 to 4.57) | 0.75 (0.21 to 2.77) | 1.59 (0.94 to 2.68) |
| Opioid, NOS | 1.97 (1.21 to 3.19) | 1.32 (0.68 to 2.58) | 1.40 (0.87 to 2.25) |
| Collapsed | 3.65 (0.71 to 18.84) | 5.37 (0.78 to 36.84) | 4.16 (1.10 to 15.78) |

** Estimate was omitted due to a cell size of 0

## Section 5.3: Discussion

This study is the first of its kind to evaluate the relationship between specific opioids and admission to a hospital from the emergency department. In addition, it provides further explanation into factors related to increased costs, as hospitalization is an especially costly component of medical care. Beyond just looking at hospitalization, this study is further strengthened by examining the nature of hospitalization and factors associated with hospitalization type.

### *Determinants of Hospitalization*

In this analysis, it was shown that heroin, methadone, morphine and unidentified opioids were associated with a significantly increased odds of admission compared to other opioids even after adjusting for patient characteristics and case type. Heroin is a drug of abuse that is frequently injected and which does not come in standard formulations, raising the risk for unintended overdoses that may be more severe. Methadone is a longer acting agent with unique pharmacokinetics that can more easily result in more severe presentations. It was also not surprising to find that visits in which opioids could not be specifically identified were more likely to result in hospitalization. These cases may be those where patients present more severely and are unable to give a verbal account of the offending opioid.

Somewhat surprisingly, morphine was associated with greater odds of hospitalization compared to all other opioids as morphine is considered to be less potent than other opioid analgesics. It was suspected that morphine might be injected more often compared to other opioids. The route of administration was compared between morphine and all other opioid analgesic types. Morphine was injected in 6.4% of cases in the sample compared to 2.7% for all

other opioid analgesics. Whether or not this indeed contributed to the higher odds of hospitalization for these patients was not formally tested. Nonetheless, it may provide a clue for why morphine patients were more likely to be hospitalized.

Age- and sex-related differences in hospitalization were also interesting. Compared to those younger than 18 years of age, those aged 18 to 34 years had lower odds of admission, all else constant. This may be due to differences in the severity of presentations or may be due to the need to hospitalize minors for other social-related reasons. As expected, those greater than 65 years of age had greater odds of hospitalization than those less than 18 years of age. Older age can render the effects of opioids and other drugs less predictable and may need closer monitoring to ensure the patients' safety. Males were associated with greater odds of hospitalization than with females. Males have been shown to have higher mortality compared to females among patients that present to the ED due to nonmedical use of opioids despite comparable ED use.[130] This suggests that males may use these agents in a riskier manner compared to females.

No differences were found with respect to race, except for Hispanics/Latinos, who had lower odds of hospitalization compared to whites. The reason for this is unclear. Clinically, race or ethnicity is unlikely to be a reason for deciding to admit patients. The difference found with respect to Hispanics or Latinos is more likely due to unobserved confounders, such as insurance status. In 2009, approximately 32% of Hispanics were uninsured compared to 12% of non-Hispanic whites.[198] Providers in the ED may be less willing to admit patients without insurance due to the high costs of hospitalization. Therefore, they may try to manage patients with less severe presentations on an outpatient basis instead of admitting them.

Cases of suicide attempt had the greatest odds of admission compared to the "other" category. Patients with suicidal ideation who have attempted suicide represent higher risk patients that need to be closely monitored and treated with psychiatric care. Furthermore, it is possible that patients who intentionally overdose may consume more of the drug than medically appropriate or even more than amounts used for abuse. It is therefore unsurprising that these types of patients have the highest likelihood of admission. Cases of overmedication were also more likely to result in admission compared to case types of "other". Cases of overmedication are invariably cases where agents prescribed for the individual were taken in greater amounts than medically appropriate, whereas cases in the "other" category are more heterogeneous (some may present due to withdrawal, others due to abuse-related behaviors, and others for toxicity). This is an important finding, especially when one considers that this is in comparison to those in the "other" case type category (most of which are abuse-related). Patients that overdose on their own medications that were prescribed to them had greater odds of hospitalization compared to abusers ("other" category).

*Determinants of Hospitalization Type among Admitted Patients*

A few interesting results were found when evaluating hospital type. In the adjusted analysis, hydrocodone, methadone, morphine, and fentanyl all had greater odds of ICU admission than having an "other" admission, compared to all other opioids, all other things constant. Heroin was not associated with ICU disposition, and is at odds with results from Specific Aim II, which showed greater costs for heroin compared to prescription opioids. This may be due to differences in the sample, as this sample may contain individuals who do not present for poisoning. Additionally, if those with ICD-9-CM diagnoses for poisoning are systematically different from those without, then this may explain some of the differences in

findings. Methadone and morphine were associated with greater odds of being hospitalized in the ICU. These results are consistent with the previous findings that showed that both are associated with increased odds of hospitalization and with the discussion that they may be related to the severity of presentation. The finding for methadone is also consistent with findings from Specific Aim II, in which it was found that methadone was associated with greater costs and LOS. Fentanyl was not shown to be a predictor of hospitalization in the analysis evaluating the probability of admission, but among those that were admitted, fentanyl patients had greater odds of ICU admission instead of an "other" admission, compared to all other opioids. This indicates that among opioid-related ED visits that merit admission to a hospital, fentanyl patients have a more severe presentation. This is consistent with its pharmacological properties, as it is the most potent opioid analgesic with long acting formulations that can increase the risk of a severe overdose. It was interesting to find that among all patients admitted for opioid use, hydrocodone patients had greater odds of hospitalization in the ICU than in "other" units. The results for this are unclear as oxycodone is a similarly used agent that is considered to be more potent than hydrocodone. Given the lack of face validity of this finding, the interpretability is limited. Finally, unspecified opioids (i.e., opioids NOS) were associated with greater odds of ICU admission instead of admission to "other" units. This is likely because those these patients represent those who are unable to give a history of their drug use due to severe presentations.

Increasing age was associated with decreased odds of hospitalization in the ICU vs. "other" units. This is in contrast to the previous findings, which found those greater than 65 had the highest odds of hospitalization. Though these patients are at a higher risk of hospitalization, they had lower odds of hospitalization in an ICU unit among all admitted patients than younger individuals. While this may seem counterintuitive, it indicates that older individuals have a

lower threshold in the severity of presentation required for hospitalization. Patients admitted for suicide had greater odds of ICU admission vs. "other" admission compared to patients with a case type of "other". Cases of suicide are likely to represent more severe presentations that require closer monitoring. In contrast, patients that visited the ED due to an "adverse reaction" had the lowest odds of ICU admission vs. "other" admission. This seems to indicate that those classified as having adverse reactions experience mild symptoms that are less likely to merit close monitoring.

Heroin patients had greater odds of hospitalization in a psychiatric or detoxification unit instead of "other " units compared to all other opioids. It is important to remember that not all cases of prescription opioid analgesic related ED-visits are necessarily due to abuse. Conversely, all heroin patients would be considered as abusers as heroin is an illicit drug with no approved medical uses. Thus, it would be expected that these patients would be more likely to be hospitalized in detoxification or chemical dependency units compared with prescription opioids. Relative to "other" admissions, codeine was shown to be less likely to result in a psychiatric/detoxification admission compared to all other opioids. This finding is consistent with the pharmacological properties of the drug as codeine is a weak opioid that has a lower potential for abuse.

A similar pattern as was seen with the ICU units was observed with respect to age and admission to a psychiatric or detoxification clinic. Increased age was associated with decreased odds of admission into these units, compared to "other" units. This indicates that older individuals are more likely to be hospitalized in these "other" units for more general reasons in order to monitor their care. In 2009, it was reported that illicit drug use was highest for those aged 18-20 (22.2%) and lowest for those aged 65 years and older (0.9%).[191] As older individuals

are less likely to engage in drug abuse compared to younger individuals, they are thus are less likely to need psychiatric/detoxification care. Similar to findings with the ICU admissions, cases of suicide were associated with greater odds of admission to a psychiatric or detoxification unit and adverse reactions were associated with lower odds when compared to the "other" case type category (i.e., abusers). Clearly, attempts at suicide would result in an increased need for psychiatric observation over an admission into "other" units. Adverse reactions, by definition, were those that resulted from normally approved uses of the drug. These cases are therefore less likely to be cases of abuse that require psychiatric or chemical dependency care.

The significance of transfers is unclear. It was assumed that a transfer meant that the patient would get transferred from the ED to an inpatient unit elsewhere. Transfers may occur because of the lack of beds in a particular hospital or quite possibly for the lack of services needed to treat the patient for the given condition. For example, some hospitals may be ill equipped to handle providing care related to detoxification or chemical dependency. Others may not be able to handle severe cases that require close monitoring in the ICU. Whatever the case may be, this category is likely to represent complex patients that likely require specialized care elsewhere.

Oxycodone and methadone were both associated with a greater odds of transfer compared to other opioids instead of being admitted to the same hospital in an "other" unit. Reasons for this are also unclear. If transfers represented those with greater complexity of care, one might expect similar findings for transfers as was found in either the ICU or psychiatric/detoxification units. However, there was no clear congruence with either the ICU admissions or psychiatric/detoxification admissions. Interpretability of these findings is limited as there does not seem to be a plausible explanation for these findings.

Older age was also associated with decreased odds of transfer, similar to patterns noted for ICU admissions or psychiatric and detoxification units. This reinforces the suspicion that older individuals are more likely to be hospitalized for general reasons rather than for specific needs (e.g., ICU or psychiatric/detoxification units). The only race-related association found to be significant in the adjusted regression was for blacks compared to whites. Blacks had lower odds of transfer compared to whites. This finding may be a spurious association as plausible explanations are difficult to gather and the confidence interval approaches one. Suicide attempts and adverse reactions were found to have similar directions of effect for transfers as was seen with ICU and psychiatric or detoxification admissions. This would be expected as suicide attempts represent more complex cases while adverse reactions represent less complex cases.

*Limitations*

This study carries several limitations. First, this was an exploratory, cross-sectional study with multiple comparisons across different variables. The level of significance was not adjusted to account for this multiplicity, increasing the chance for Type I error for any given variable. Because this was an exploratory study intended to generate hypotheses, it was chosen to leave the significance level unadjusted.

Second, descriptions of symptoms were not available in the dataset. This made it impossible to determine whether cases were due to poisoning or due to other reasons. In Specific Aim I, different combinations of case definitions were used to define likely cases of poisoning. The base case scenario assumed a more conservative definition, excluding those who were referred or admitted to detoxification clinics or units. In this aim, a more liberal approach was used to capture all potential cases of poisoning. For example, all cases were used despite

being admitted to psychiatric and detoxification units. In addition, cases of adverse reactions were included. This was done since the presentation of poisoning does not preclude one from being admitted or referred to detoxification or chemical dependency clinics or units. Depending on the opioid in question, opioid poisoning can be rapidly reversed. In addition, naloxone may induce withdrawal symptoms necessitating detoxification treatment. The only explicit restriction imposed with regards to case type was for those that were actively seeking detoxification, in which case were unlikely to represent true poisoning cases. Adverse reactions were included as symptoms of poisoning may occur despite appropriate use of the drug. However, one should note that adverse reactions may also include other symptoms such as hypersensitivity reactions or chronic side effects of the opioids such as constipation.

Third, diagnoses were unavailable. Diagnoses would have been helpful to better classify cases based upon their symptoms. It would also help to adjust for comorbidities that may act as confounders to the outcome. Although reporting diagnoses would be helpful analytically, the inclusion of such would also be limited regardless. Recording of comorbidities and other diagnoses would not be as robust or complete as in an inpatient setting. Thus, it was difficult to adjust for comorbidities in ED settings where data were retrospectively obtained.

Fourth, payer information was not collected. Providers may be less willing to admit a patient who does not have insurance to avoid incurring high costs. For these patients, outpatient management would result in a decreased financial burden for the patient and for the hospital. This was one potential explanation for why Hispanics were shown to be less likely to be hospitalized compared to whites. This was unable to be assessed due to the lack of availability of insurance information.

Fifth, many patients fell into the case type category of "other". This was because information collected in the chart reviews were often lacking in terms of the details for the context in which these events occurred. Because of this, many types of patients are included in the "other" category, which may include patients with withdrawal symptoms as well as those with intoxication. It was therefore not possible to separate cases of intoxication from those with other symptoms unrelated to poisoning.

Finally, patients hospitalized to a unit with combined psychiatric and detoxification units were classified as "other" admissions as well. Those hospitalized to either psychiatric or detoxification units that were separated were classified as a "psychiatric/detoxification" unit. Because of this limitation, the effect of being admitted to a psychiatric or detoxification unit may be understated since "other" was the referent group.

In conclusion, hospitalization was found to depend on specific opioids, even after adjusting for various patient characteristics. Heroin, methadone, and morphine were associated with greater odds for hospitalization. Among admitted patients, morphine, fentanyl and methadone were associated with the greatest odds of ICU admission. Heroin was found to be positively associated with psychiatric/detoxification admissions, while codeine was negatively associated with psychiatric admissions.

# Chapter VI:

## Summary & Conclusions

Opioid poisoning is an important public health problem that has increased significantly in the past decade. Naloxone prescription programs have been initiated across the country to better address this issue and to prevent and reverse opioid poisoning and related mortality. Although previous studies have attempted to quantify the economic burden associated with opioid abuse, none have focused on opioid poisoning. The first aim of this dissertation focused on quantifying the economic burden of opioid poisoning in terms of direct and indirect costs to society. It is estimated to cost society $20.4 billion annually, most of which is related to mortality costs. Approximately $2.2 billion dollars of this estimate are due to direct costs, incorporating ambulance costs, emergency department costs, naloxone prescription costs, and inpatient costs. The greatest mortality costs were for methadone, followed by oxycodone and hydrocodone. The greatest economic impacts can be realized through the prevention of opioid poisoning mortality.

In addition to quantifying the economic burden of opioid poisoning, it is also important to dig deeper to understand the relationship with different characteristics with increased costs in this population. The second aim of this study focused on evaluating the relationship between opioid type and costs, length of stay, and in-hospital mortality. Heroin, methadone and "unspecified" opioids were associated with the greatest costs compared to prescription opioids. An effect was also seen with length of stay, with methadone associated with a greater length of stay compared to prescription opioids. Patients with heroin or unspecified poisoning were most

likely to die in-hospital from opioid poisoning, though patients with methadone poisoning were no more likely to experience in-hospital mortality compared to heroin or prescription opioids.

The third aim of this study evaluated specific opioids and their propensity to result in hospitalization. It also looked beyond just hospitalization and evaluates differences in the types of admission among admitted patients. This is important as the type of hospitalization can have implications for cost (i.e., ICU care associated with greater costs). It can also shed light on the types of issues that are being addressed among patients in the hospital. Patients in the ED due to heroin, methadone, morphine, and unspecified opioids were more likely to result in hospitalization. Among those that were hospitalized, visits involving heroin, methadone, morphine and unspecified opioids had greater odds of hospitalization in the ICU, while heroin was more likely to result in a psychiatric or detoxification admission. The effect of age was interesting, with greater odds of hospitalization with increasing age, but lower odds of ICU admission versus "other" admissions with increasing age, indicating that there are more "precautionary" admissions for older adults. Cases of "overmedication" (i.e., those who took more of their own prescribed medication) were more likely to be hospitalized compared to cases of "other."

In each of these analyses, there were recurring themes. One is the potential high cost of methadone poisoning relative to other types of opioid poisoning. Methadone is implicated in the largest share of mortality costs relative to other prescription opioids. It is a predictor of hospitalization, ICU admission, greater hospitalization costs, and greater length of stay. Age was a predictor of hospitalization and was associated with greater hospital costs, length of stay, and in-hospital mortality. Male gender was associated with increased costs and LOS and a greater odds of hospitalization and in-hospital mortality.

The information produced from these results can help to provide a rationale for funding interventions designed to prevent or reverse opioid poisoning. Given the high costs associated with methadone-related mortality and the increased costs associated with methadone in the hospital setting, it makes sense to target this population. Heroin-dependent individuals are commonly treated for their dependence in methadone clinics, but use of methadone is especially risky. Although the risk associated with methadone is well known, these findings confirm the risk associated with the use of methadone. This should not discount, however, the potential benefit for such interventions to also target those at high risk of prescription opioid abuse with other opioids.

Future research should evaluate those in the "at-risk" population to evaluate types of patients most likely to experience a poisoning event. The research in this dissertation evaluates predictors of increased costs once a poisoning event has occurred, but does not evaluate the likelihood of experiencing opioid poisoning in a cohort of prescription opioid misusers and abusers. Evaluating the likelihood of experiencing opioid poisoning among those who are at risk of poisoning should further aid in identifying specific populations on which to focus intervention efforts.

More efforts need to be realized to fully characterize true opioid poisoning. Neither DAWN nor HCUP provided the ideal data needed to identify patients with opioid intoxication. Work should focus on assessing the sensitivity and specificity of available ICD-9-CM codes and/or specifically characterizing drug-related ED visits in DAWN depending on symptoms or diagnoses.

Finally, evaluation of the costs associated with the provision of naloxone prescription intervention efforts should be performed. Assessing the costs of providing such programs

against the costs of opioid poisoning can help in determining the value of these programs. Costs should incorporate those related to naloxone, education, medical and administrative personnel, facility costs, and other costs related to the provision of these services.

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# Appendix A

**Costs per Event Calculation*:**

Direct Cost per Event:

$$DC_{event} = (\bar{c}_{ed} + \bar{c}_{phy})\left(\frac{p_{ed}}{p_{ed} + p_{ip} + p_{mor}}\right) + (\bar{c}_{ip})\left(\frac{p_{ip}}{p_{ed} + p_{ip} + p_{mor}}\right) + (\bar{c}_{amb})(pct_{amb})\left(\frac{p_{ip} + p_{ed}}{p_{ed} + p_{ip} + p_{mor}}\right)$$

Indirect Cost per Event:

$$IC_{event} = \left(\bar{c}_{ed_{abs}}\right)\left(\frac{p_{ed}}{p_{ed} + p_{ip} + p_{mor}}\right) + \left(\bar{c}_{ip_{abs}}\right)\left(\frac{p_{ip}}{p_{ed} + p_{ip} + p_{mor}}\right) + (\bar{c}_{mor})\left(\frac{p_{mor}}{p_{ed} + p_{ip} + p_{mor}}\right)$$

Total Cost per Event:

$$TC_{event} = DC_{event} + IC_{event}$$

| | | |
|---|---|---|
| $\bar{c}_{ed}$ | = | mean estimated treatment cost for ED treat-and-release visits |
| $\bar{c}_{phy}$ | = | mean estimated ED physician reimbursement |
| $\bar{c}_{ip}$ | = | mean estimated treatment cost for inpatient discharges |
| $\bar{c}_{amb}$ | = | mean cost for ambulance transport |
| $\bar{c}_{ed_{abs}}$ | = | mean absenteeism cost for ED treat-and-release visits |
| $\bar{c}_{ip_{abs}}$ | = | mean absenteeism cost for inpatient discharges |
| $\bar{c}_{mor}$ | = | mean mortality cost |
| $p_{ed}$ | = | prevalence of ED treat-and-release visits |
| $p_{ip}$ | = | prevalence of inpatient discharges |
| $p_{mor}$ | = | prevalence of mortality |
| $pct_{amb}$ | = | percent transported by ambulance |

*To avoid double counting events in the ED and inpatient setting that resulted in death, the weighted number of deaths obtained through DAWN was subtracted from the total sum of all events (i.e., denominator) for heroin (n = 683) and prescription opioids (n = 1,682) and all opioids (n = 2,365).

## Appendix B

As a limitation, NEDS does not provide the same categories of hospital characteristics as reported in this report. The classifications provided in NEDS and the urban/rural classification are provided in Table B.2. Hospital control is defined in NEDS as 1) government or private, collapsed category, 2) private, non-profit, voluntary, 3) private, invest-own, 4) private, collapsed category. Because bed size was not available in the NEDS dataset, this attribute could not be considered when assigning CCRs. As HCUP does not provide the equivalent distinct classifications as reported, certain CCRs had to be combined and weighted based on the reported sample sizes. For example, to assign a CCR to the rural/government category in NEDS, the sample sizes in the report for "rural, low volume, government" and "rural, non-low volume, government" were used to estimate a combined weighted CCR for "rural, government". Using the provided numbers this is calculated as the following:

$$\frac{41}{(41+70)} * 0.570 + \frac{70}{(41+70)} * 0.527 = 0.543$$

The same basic procedures were used to calculate weighted CCRs in accordance with the classifications provided by HCUP. The final CCRs used to convert charges to costs are provided in Table B.3.

**Table B.1: 2003 ED Cost-to-Charge Ratios (CCRs) Provided by HCUP**

| | n | Weighted mean CCR |
|---|---|---|
| Rural, Low volume, Gov't | 41 | 0.570 |
| Rural, low volume, PNFP or Prof | 33 | 0.571 |
| Rural, non-low volume, Gov't | 70 | 0.527 |
| Rural, non-low volume, PNFP | 110 | 0.529 |
| Rural, non-low volume, Profit | 42 | 0.361 |
| Urban, Gov't | 30 | 0.457 |
| Urban, PFNP | 185 | 0.552 |
| Urban, Profit | 46 | 0.395 |
| All | 556 | 0.514 |

PNFP = private, not for profit; Gov't = government; Prof = for profit

**Appendix B, continued**

**Table B.2: HCUP NEDS Classifications of Urban/Rural Status**

| HCUP Classifications | Urban/rural classification |
|---|---|
| 1) Large metropolitan areas with at least 1 million residents | Urban |
| 2) Small metropolitan areas with less than 1 million residents | Urban |
| 3) Micropolitan areas | Urban |
| 4) Not metropolitan or micropolitan | Rural |
| 5) Metropolitan, collapsed category of large and small metropolitan | Urban |
| 6) Non-metropolitan, collapsed category of micropolitan and rural | Rural |

Urban/rural classification based on U.S. Census Definitions[199]

**Table B.3: Calculated ED CCRs**

| | CCR |
|---|---|
| Rural, gov't or private (collapsed) | 0.515 |
| Rural, Gov't | 0.543 |
| Rural, PNFP | 0.537 |
| Rural, For profit | 0.385 |
| Rural, private collapsed | 0.498 |
| Urban, gov't or private (collapsed) | 0.513 |
| Urban, Gov't | 0.457 |
| Urban, PNFP | 0.552 |
| Urban, Prof | 0.395 |
| Urban, private collapsed | 0.521 |

PNFP = private, no for profit,
Gov't = government

# Appendix C

**Table C.1: Parameter Estimates for Elixhauser Comorbidities in Costs Model**

| Parameter | β | SE | Exp(β) | Z | p-value |
|---|---|---|---|---|---|
| HIV/AIDS | -0.037 | 0.1032 | 0.96 (0.79 to 1.18) | 0.13 | 0.8944 |
| Alcohol | 0.004 | 0.0283 | 1.00 (0.95 to 1.06) | 0.13 | 0.8944 |
| Anemia | 0.287 | 0.0342 | 1.33 (1.25 to 1.42) | 8.41 | < 0.0001 |
| Arthritis | 0.126 | 0.0688 | 1.13 (0.99 to 1.30) | 1.84 | 0.0662 |
| Blood loss | 0.384 | 0.1681 | 1.47 (1.06 to 2.04) | 2.28 | 0.0225 |
| Congestive heart failure | 0.253 | 0.0429 | 1.29 (1.18 to 1.40) | 5.89 | < 0.0001 |
| Chronic lung disease | 0.079 | 0.0252 | 1.08 (1.03 to 1.14) | 3.12 | 0.0018 |
| Coagulation disorder | 0.529 | 0.056 | 1.70 (1.52 to 1.90) | 9.31 | < 0.0001 |
| Depression | -0.076 | 0.0279 | 0.93 (0.88 to 0.98) | -2.72 | 0.0066 |
| Diabetes | -0.007 | 0.0317 | 0.99 (0.93 to 1.06) | -0.23 | 0.8198 |
| Diabetes, with CC | 0.061 | -0.129 | 0.99 (0.88 to 1.12) | -0.16 | 0.8748 |
| Drug Abuse | 0.030 | 0.0255 | 1.03 (0.98 to 1.08) | 1.16 | 0.2479 |
| Hypertension | -0.006 | 0.0240 | 0.99 (0.95 to 1.04) | -0.24 | 0.8085 |
| Hypothyroidism | -0.22 | 0.0328 | 0.98 (0.92 to 1.04) | -0.68 | 0.4957 |
| Liver | -0.031 | 0.0464 | 0.97 (0.92 to 1.04) | -0.66 | 0.5094 |
| Lymphoma | 0.401 | 0.1806 | 1.49 (1.05 to 2.13) | 2.22 | 0.0263 |
| Fluid/Electrolytes | 0.415 | 0.0233 | 1.51 (1.45 to 1.59) | 17.84 | < 0.0001 |
| Metastatic cancer | 0.168 | 0.1003 | 1.18 (9.97 to 1.44) | 1.67 | 0.094 |
| Neurological disorder | -0.081 | 0.0274 | 0.92 (0.87 to 0.97) | -2.97 | 0.0030 |
| Obesity | 0.207 | 0.0359 | 1.23 (1.15 to 1.32) | 5.77 | < 0.0001 |
| Paralysis | 0.362 | 0.0841 | 1.44 (1.22 to 1.70) | 4.32 | < 0.0001 |
| Peripheral vascular | 0.178 | 0.0731 | 1.20 (1.04 to 1.38) | 2.44 | 0.0148 |
| Psychiatric | 0.011 | 0.0256 | 1.01 (0.96 to 1.06) | 0.42 | 0.6742 |
| Pulmonary circulation | 0.404 | 0.0723 | 1.50 (1.300 to 1.73) | 5.59 | < 0.0001 |
| Renal Failure | 0.122 | 0.0548 | 1.13 (1.02 to 1.26) | 2.24 | 0.0252 |
| Tumor | 0.004 | 0.0889 | 1.00 (0.84 to 1.19) | 0.04 | 0.9659 |
| Ulcer | -0.388 | 0.1840 | 0.67 (0.47 to 0.97) | -2.13 | 0.035 |
| Valve | 0.133 | 0.066 | 1.14 (1.00 to 1.30) | 2.02 | 0.0432 |
| Weight Loss | 0.747 | 0.0874 | 2.11 (1.78 to 2.50) | 8.54 | < 0.0001 |

## Appendix C, continued

**Table C.2: Parameter Estimates for Elixhauser Comorbidities in LOS Model**

| Parameter | β | SE | Exp(β) | Z | p-value |
|---|---|---|---|---|---|
| HIV/AIDS | 0.031 | 0.1023 | 1.03 (0.84 to 1.26) | 0.3 | 0.7646 |
| Alcohol | 0.043 | 0.0301 | 1.04 (0.98 to 1.11) | 1.42 | 0.1543 |
| Anemia | 0.265 | 0.0319 | 1.30 (1.22 to 1.39) | 8.30 | < 0.0001 |
| Arthritis | 0.066 | 0.0655 | 1.07 (0.94 to 1.21) | 1.01 | 0.3119 |
| Blood loss | 0.453 | 0.1704 | 1.57 (1.13 to 2.20) | 2.66 | 0.0079 |
| Congestive heart failure | 0.186 | 0.0454 | 1.20 (1.10 to 1.32) | 4.10 | < 0.0001 |
| Chronic lung disease | 0.057 | 0.0270 | 1.06 (1.00 to 1.12) | 2.12 | 0.0339 |
| Coagulation disorder | 0.412 | 0.0558 | 1.51 (1.35 to 1.68) | 7.38 | < 0.0001 |
| Diabetes | -0.042 | 0.0367 | 0.96 (0.89 to 1.03) | -1.14 | 0.2550 |
| Diabetes with complications | -0.0274 | 0.0551 | 0.97 (0.87 to 1.08) | -0.50 | 0.6191 |
| Depression | -0.109 | 0.0279 | 0.90 (0.85 to 0.95) | -3.9 | < 0.0001 |
| Drug Abuse | 0.076 | 0.0272 | 1.08 (1.02 to 1.14) | 2.81 | 0.0049 |
| Hypertension | -0.005 | 0.026 | 1.00 (0.95 to 1.05) | -0.18 | 0.8555 |
| Hypothyroidism | -0.029 | 0.0349 | 0.97 (0.91 to 1.04) | -0.82 | 0.4134 |
| Liver | 0.013 | 0.0498 | 1.01 (0.92 to 1.12) | 0.27 | 0.7850 |
| Lymphoma | 0.170 | 0.1816 | 1.18 (0.83 to 1.70) | 0.93 | 9.3503 |
| Fluid/Electrolytes | 0.301 | 0.0231 | 1.35 (1.29 to 1.41) | 13.03 | < 0.0001 |
| Metastatic cancer | 0.1712 | 0.0813 | 1.19 (1.01 to 1.39) | 2.10 | 0.0354 |
| Neurological disorder | -0.067 | 0.0280 | 0.94 (0.89 to 0.99) | -2.38 | 0.0173 |
| Obesity | 0.184 | 0.0351 | 1.20 (1.12 to 1.29) | 5.24 | < 0.0001 |
| Paralysis | 0.495 | 0.1022 | 1.64 (1.34 to 2.00) | 4.85 | 0.0001 |
| Peripheral vascular | 0.109 | 0.0699 | 1.12 (0.97 to 1.28) | 1.56 | 0.1191 |
| Psychosis | 0.041 | 0.0284) | 1.04 (0.99 to 1.10) | 1.44 | 0.1488 |
| Pulmonary circulation | 0.324 | 0.0654 | 1.38 (1.22 to 1.57) | 4.95 | < 0.0001 |
| Renal Failure | 0.148 | 0.0495 | 1.16 (1.05 to 1.28) | 3.00 | 0.0027 |
| Tumor | 0.055 | 0.1005 | 1.05 (0.87 to 1.29) | 0.55 | 0.5838 |
| Ulcer | -0.548 | 0.2573 | 0.58 (0.35 to 0.96) | -2.13 | 0.0334 |
| Valve | 0.148 | 0.0678 | 1.16 (1.02 to 1.32) | 2.19 | 0.0287 |
| Weight Loss | 0.659 | 0.0621 | 1.93 (1.71 to 2.18) | 10.62 | < 0.0001 |

## Appendix C, continued

**Table C.3: Parameter Estimates for Elixhauser Comorbidities in Mortality Model**

| Parameter | OR | SE | 95% CI | $\chi^2$ | p-value |
|---|---|---|---|---|---|
| HIV/AIDS | 1.78 | 1.282 | 0.43 to 7.30 | 0.64 | 0.4232 |
| Alcohol | 0.92 | 0.155 | 0.66 to 1.28 | 0.23 | 0.6630 |
| Anemia | 1.42 | 0.247 | 1.01 to 2.00 | 4.12 | 0.0423 |
| Arthritis | 1.13 | 0.474 | 0.50 to 2.57 | 0.09 | 0.7705 |
| Blood loss | 1.54 | 1.135 | 0.36 to 6.53 | 0.34 | 0.5611 |
| Congestive heart failure | 1.11 | 0.276 | 0.68 to 1.81 | 0.17 | 0.6823 |
| Chronic lung disease | 1.07 | 0.177 | 0.77 to 1.48 | 0.16 | 0.6935 |
| Coagulation disorder | 0.20 | 0.036 | 0.14 to 0.29 | 82.3 | < 0.0001 |
| Depression | 1.72 | 0.292 | 1.23 to 2.40 | 10.2 | 0.0014 |
| Diabetes | 1.35 | 0.287 | 0.89 to 2.05 | 2.00 | 0.1573 |
| Diabetes with complications | 3.65 | 1.89 | 1.32 to 10.09 | 6.25 | 0.0124 |
| Drug Abuse | 1.87 | 0.273 | 1.40 to 2.49 | 18.2 | < 0.0001 |
| Hypertension | 1.23 | 0.196 | 0.90 to 1.68 | 1.63 | 0.2021 |
| Hypothyroidism | 1.58 | 0.480 | 0.87 to 2.87 | 2.27 | 0.1315 |
| Liver | 1.12 | 0.317 | 0.64 to 1.95 | 0.16 | 0.6888 |
| Lymphoma | 0.73 | 0.555 | 0.16 o 3.24 | 0.17 | 0.6778 |
| Fluid/Electrolytes | 0.34 | 0.044 | 0.27 to 0.44 | 68.9 | < 0.0001 |
| Metastatic cancer | 0.21 | 0.055 | 0.12 to 0.35 | 34.9 | < 0.0001 |
| Neurological disorder | 1.17 | 0.177 | 0.87 to 1.56 | 1.12 | 0.2902 |
| Obesity | 1.20 | 0.313 | 0.72 to 2.00 | 0.51 | 0.4767 |
| Paralysis | 1.40 | 0.736 | 0.50 to 3.92 | 0.42 | 0.5183 |
| Peripheral vascular | 0.57 | 0.190 | 0.29 to 1.09 | 2.86 | 0.0910 |
| Psychosis | 2.90 | 0.573 | 1.96 to 4.27 | 28.8 | < 0.0001 |
| Pulmonary circulation | 0.37 | 0.133 | 0.18 to 0.74 | 7.70 | 0.0055 |
| Renal Failure | 0.65 | 0.148 | 0.41 to 1.01 | 3.60 | 0.0579 |
| Tumor | 0.43 | 0.193 | 0.18 to 1.03 | 3.55 | 0.0594 |
| Ulcer | 0.07 | 0.036 | 0.03 to 0.19 | 28.7 | < 0.0001 |
| Valve | 1.52 | 0.713 | 0.60 to 3.81 | 0.79 | 0.3740 |
| Weight Loss | 0.66 | 0.179 | 0.39 to 1.13 | 2.31 | 0.1286 |

# Appendix D

**Table D.1: ICD-9-CM Codes for Select Opioid Abuse-Related Comorbidities**

| | |
|---|---|
| Sedative/hypnotic/anxiolytic involvement | 304.1X, 305.4X, 967.X, 969.4 |
| Involvement of other drugs of abuse | 305.2 – .3, 305.6 – .9, 969.0 – .3, 969.5 – .9 |
| Endocarditis | 421.x |
| Skin infections | 680.x – 686.x |
| Gastrointestinal bleed | 578.x |
| Pancreatitis | 577.0, 577.1 |
| Sexually transmitted infection | 090.0 – 099.9 |
| Herpes simplex | 054.X |
| Burns | 940.X – 949.X |
| Trauma | 800.X – 904.X, 910.X – 939.X, 959.X |
| Motor vehicle accidents | E810.X – E819.X |
| Cancer | 140.X – 239.X, 338.3, V10.X |
| Back/neck pain | 724.2, 724.5, 723.1 |
| Acute pain NOS | 338.1 |
| Chronic pain NOS | 338.2 |
| Neuropathic pain | 350.1-.9, 353.0-.9, 354 - 355, 357.1,.4-.9, 053.13, 072.72 |
| Headache/migraine | 339.0-.8, 346.0-.9 |
| Suicide | E950 – E959 |

**Appendix D, continued**

**Table D.2: Comparison of Prevalence (%) for Select Comorbidities by Opioid Type**

| | Heroin n = 1,410 | Methadone n = 1,699 | Prescription Opioid n = 6,783 | Unspecified n = 3,770 | p-value |
|---|---|---|---|---|---|
| Sedative/hypnotic/ anxiolytic involvement | 17.3 | 35.6 | 30.7 | 43.5 | < 0.0001 |
| Alcohol involvement | 26.7 | 15.9 | 14.9 | 17.6 | < 0.0001 |
| Involvement of other drugs of abuse | 36.2 | 27.6 | 22.6 | 30.5 | < 0.0001 |
| Endocarditis | 0.3 | 0.1 | 0.1 | 0.1 | 0.1650 |
| Skin infections | 4.0 | 2.2 | 2.3 | 2.1 | 0.0003 |
| Gastrointestinal bleed | 1.1 | 1.2 | 1.2 | 1.0 | 0.7783 |
| Pancreatitis | 0.6 | 2.0 | 1.5 | 1.4 | 0.0149 |
| Sexually transmitted infection | 0.1 | 0.1 | 0.2 | 0.1 | 0.2971 |
| Herpes simplex | 0.1 | | | | 0.1254 |
| Burns | 0.07 | 0.12 | 0.19 | 0.21 | 0.7799 |
| Trauma | 5.4 | 4.1 | 5.9 | 5.6 | 0.0471 |
| Motor vehicle accidents | 0.5 | 0.2 | 0.3 | 0.3 | 0.4461 |
| Back/neck pain | 3.6 | 15.3 | 16.6 | 14.1 | < 0.0001 |
| Acute pain NOS | 0.0 | 0.2 | 0.3 | 0.1 | 0.0829 |
| Chronic pain NOS | 2.3 | 15.9 | 13.2 | 15.9 | < 0.0001 |
| Neuropathic pain | 1.0 | 1.1 | 1.8 | 1.6 | 0.0444 |
| Headache/migraine | 0.5 | 1.8 | 3.3 | 3.0 | < 0.0001 |
| Suicide | 19.6 | 20.2 | 33.9 | 28.1 | < 0.0001 |

Pearson's $\chi^2$ was used to test differences in frequency.

## Appendix D, continued

**Table D.3: Costs by Presence of Select Comorbidities**

| | Present, $ (SD) | Not Present, $ (SD) | p-value |
|---|---|---|---|
| Sedative/hypnotic/anxiolytic involvement | 8,744 (12,108) | 10,316 (15,598) | < 0.0001 |
| Alcohol involvement | 9,779 (13,048) | 8,797 (14,840) | 0.9582 |
| Involvement of other drugs of abuse | 8,906 (13,213) | 10,112 (14,982) | < 0.0001 |
| Skin infections | 16,334 (23,467) | 9,629 (14,215) | < 0.0001 |
| Pancreatitis | 15,803 (23,075) | 9,698 (14,353) | < 0.0001 |
| Trauma | 15,491 (27,020) | 9,456 (13,386) | < 0.0001 |
| Back/neck pain | 8,427 (10,718) | 10,022 (15,086) | < 0.0001 |
| Chronic pain NOS | 8,733 (11,506) | 9,958 (14,963) | 0.0009 |
| Neuropathic pain | 11,296 (14,678) | 9,762 (14,533) | 0.1285 |
| Headache and Migraine | 8,239 (11,885) | 9,836 (14,612) | 0.0411 |
| Suicide | 7,824 (11,550) | 10,593 (15,526) | < 0.0001 |

Under the central limit theorem (t-tests are robust in large sample sizes) Student's t-test was used to compare costs (present vs. not present)

**Table D.4: LOS by Presence of Select Comorbidities**

| | Present | Not Present | p-value |
|---|---|---|---|
| Sedative/hypnotic/anxiolytic involvement | 3.5 (5.4) | 4.1 (4.2) | < 0.0001 |
| Alcohol involvement | 4.1 (6.0) | 4.0 (6.3) | 0.4062 |
| Involvement of other drugs of abuse | 3.5 (4.7) | 4.0 (5.1) | < 0.0001 |
| Skin infections | 7.2 (9.2) | 3.8 (4.9) | < 0.0001 |
| Pancreatitis | 6.1 (7.6) | 3.9 (5.0) | < 0.0001 |
| Trauma | 5.5 (6.9) | 3.8 (4.9) | < 0.0001 |
| Back/neck pain | 3.5 (4.0) | 4.0 (5.2) | 0.0005 |
| Chronic pain | 3.6 (4.3) | 3.9 (5.1) | 0.0029 |
| Neuropathic pain | 5.1 (6.3) | 3.9 (5.0) | 0.0004 |
| Headache and Migraine | 3.7 (4.6) | 3.9 (5.0) | 0.3476 |
| Suicide | 3.6 (4.3) | 4.0 (5.3) | < 0.0001 |

Under the central limit theorem, Student's t-test was used to compare LOS (present vs. not present)

**Appendix D, continued**

**Table D.5: Mortality by Presence of Select Comorbidities**

| | Present | Not Present | p-value |
|---|---|---|---|
| Sedative/hypnotic/anxiolytic involvement | 111 (2.4) | 269 (3.0) | 0.0764 |
| Alcohol involvement | 66 (17.4) | 2,249 (17.0) | 0.8316 |
| Involvement of other drugs of abuse | 95 (2.6) | 285 (2.9) | 0.4294 |
| Skin infections | 12 (3.7) | 368 (2.8) | 0.3248 |
| Pancreatitis | 5 (2.5) | 375 (2.8) | 0.8322 |
| Trauma | 20 (2.7) | 360 (2.8) | 0.8594 |
| Back/neck pain | 32 (1.6) | 348 (3.0) | 0.0008 |
| Chronic pain | 26 (1.4) | 354 (3.0) | 0.0001 |
| Neuropathic pain | 3 (1.4) | 377 (2.8) | 0.1995 |
| Headache and Migraine | 1 (0.3) | 379 (2.9) | 0.0027 |
| Suicide | 376 (1.9) | 304 (3.1) | < 0.0001 |

Pearson's $\chi^2$ test was used to compare mortality

**Table D.6: Included Conditions for Each Model Among Select Comorbidities**

| | Cost Model | LOS Model | Mortality Model |
|---|---|---|---|
| Sedative/hypnotic/anxiolytic involvement | X | X | |
| Involvement of other drugs of abuse | X | X | |
| Skin infections | X | X | |
| Pancreatitis | X | X | |
| Trauma | X | X | |
| Back/neck pain | X | X | X |
| Chronic pain NOS | X | X | X |
| Neuropathic pain | | X | |
| Headache/migraine | X | | * |
| Suicide | X | X | X |

Only select shown to be significantly different according to opioid type are shown. X indicates inclusion.

*Though significant, headache and migraine was excluded due to the very small cell size

## Appendix D, continued

**Table D.7: Parameter Estimates for Select Comorbidities in Costs Model**

| Parameter | β | SE | Exp(β) (95% CI) | Z | p-value |
|---|---|---|---|---|---|
| Sedative/hypnotic involvement | -0.006 | 0.023 | 0.99 (0.95 to 1.04) | -0.24 | 0.8105 |
| Other drug abuse | -0.027 | 0.025 | 0.97 (0.93 to 1.02) | -1.05 | 0.292 |
| Skin and soft tissue infection | 0.245 | 0.076 | 1.28 (1.10 to 1.48) | 3.21 | 0.0013 |
| Pancreatitis | 0.365 | 0.100 | 1.44 (1.19 to 1.75) | 3.67 | 0.0002 |
| Trauma | 0.360 | 0.056 | 1.43 (1.28 to 1.60) | 6.45 | < 0.0001 |
| Suicide | -0.119 | 0.023 | 0.89 (0.85 to 0.93) | -5.18 | < 0.0001 |
| Headache/migraine | 0.052 | 0.059 | 1.05 (0.94 to 1.18) | 0.87 | 0.3827 |
| Chronic pain | -0.071 | 0.028 | 0.93 (0.88 to 0.98) | -2.51 | 0.0119 |
| Back and neck pain | -0.053 | 0.028 | 0.95 (0.90 to 1.00) | -1.86 | 0.0628 |

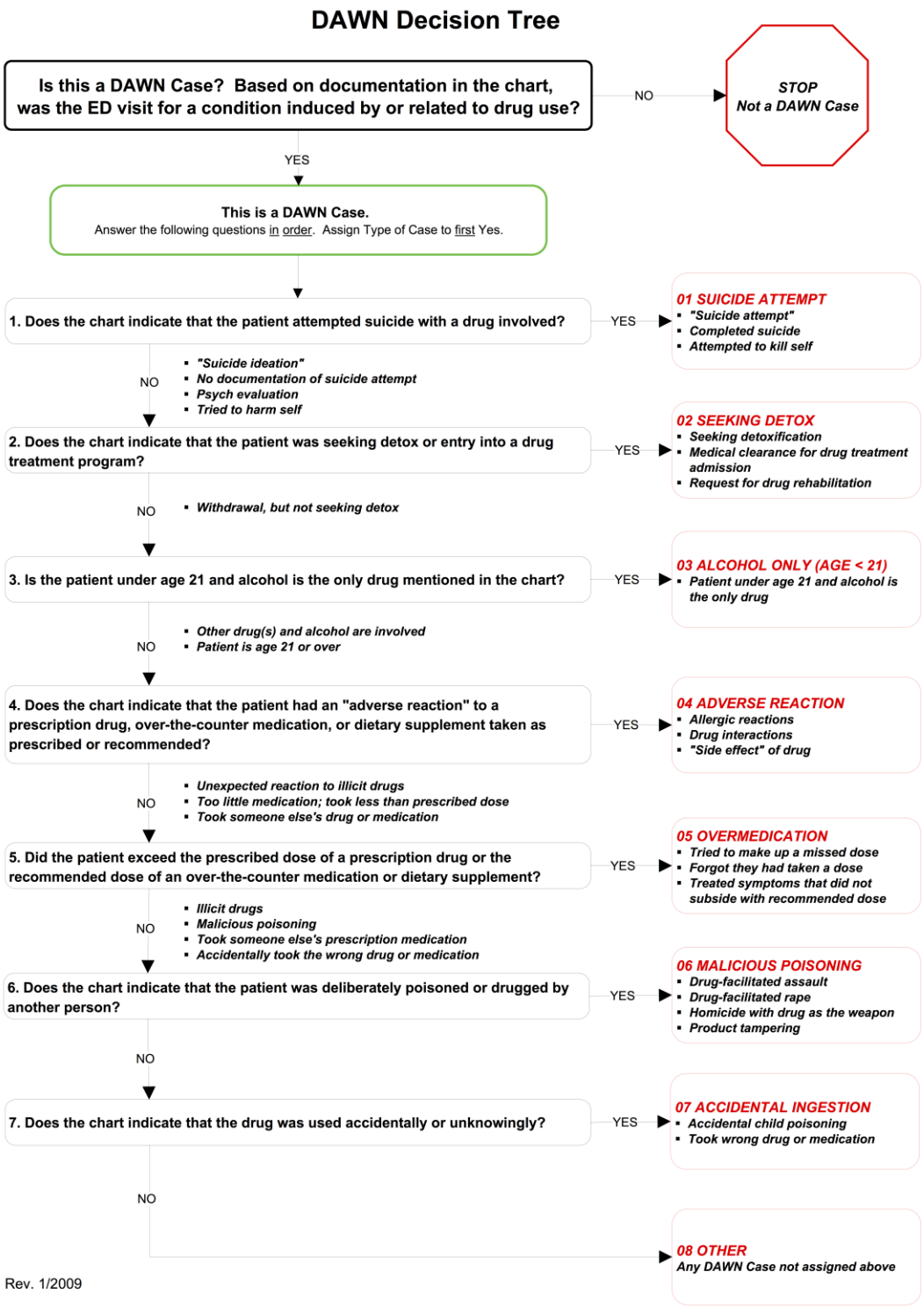
**Table D.8: Parameter Estimates for Select Comorbidities in LOS Model**

| Parameter | β | SE | Exp(β) (95% CI) | Z | p-value |
|---|---|---|---|---|---|
| Sedative/hypnotic involvement | -0.051 | 0.025 | 0.95 (0.91 to 1.00) | -2.09 | 0.037 |
| Other drug abuse | -0.080 | 0.028 | 0.92 (0.87 to 0.97) | -2.88 | 0.0039 |
| Skin and soft tissue infection | 0.384 | 0.066 | 1.47 (1.29 to 1.67) | 5.84 | < 0.0001 |
| Pancreatitis | 0.336 | 0.090 | 1.40 (1.17 to 1.67) | 3.72 | 0.0002 |
| Trauma | 0.281 | 0.042 | 1.32 (1.22 to 1.44) | 6.69 | < 0.0001 |
| Suicide | 0.063 | 0.028 | 1.07 (1.01 to 1.13) | 2.23 | 0.026 |
| Chronic pain | -0.069 | 0.033 | 0.93 (0.88 to 1.00) | -2.11 | 0.0345 |
| Back and neck pain | -0.069 | 0.033 | 0.96 (0.91 to 1.02) | -1.25 | 0.2124 |
| Neuropathic pain | 0.140 | 0.085 | 1.15 (0.97 to 1.36) | 1.65 | 0.0997 |

**Table D.9: Parameter Estimates for Select Comorbidities in Mortality Model**

| Parameter | OR | SE | 95% CI | $\chi^2$ | p-value |
|---|---|---|---|---|---|
| Suicide | 1.10 | 0.172 | 0.81 to 1.49 | 0.36 | 0.5471 |
| Chronic pain | 1.62 | 0.379 | 1.02 to 2.56 | 4.20 | 0.0403 |
| Back and neck pain | 1.20 | 0.238 | 0.81 to 1.77 | 0.81 | 0.3667 |

# Appendix E, Figure E.1: DAWN Decision Tree



**Timothy J. Inocencio**
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Email: inocenciotj@vcu.edu
Mobile: 804-687-0388

## Education

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|---|---|
| 2007 - current | Doctor of Philosophy *(expected completion in December, 2012)*<br>Virginia Commonwealth University<br>School of Pharmacy<br>Department of Pharmacotherapy and Outcomes Science |
| 2006 - current | Doctor of Pharmacy *(expected completion in December, 2012)*<br>Virginia Commonwealth University<br>School of Pharmacy<br>Department of Pharmacotherapy and Outcomes Science |
| 2004 - 2006 | Pre-pharmacy<br>Virginia Commonwealth University<br>College of Humanities and Sciences |

## Research Experiences

**2012:** The economic burden of opioid poisoning in the United States and determinants of increased costs in opioid poisoning.

*Completed a dissertation evaluating 1) the economic burden of opioid poisoning, 2) differences in length of stay, costs, and mortality between opioid types in opioid poisoning, and 3) determinants of hospitalization and admission type among patients who present to the emergency department for opioid poisoning.*

**2012:** Cost utility analysis of nilotinib compared with imatinib in newly diagnosed chronic myelogenous leukemia.

*Performed a Markov state-transition model through Microsoft Excel in collaboration with a graduate student, advisor, oncologist and clinical oncology pharmacis evaluating nilotinib compared to standard treatment imatinib in chronic myelogenous leukemia. Poster presented to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 2012 Annual Meeting.*

**Research Experiences, continued**

**2011:** National Alliance of State Pharmacy Associations (NASPA) 2011 report on persistence following refill synchronization.

*Analyzed data for a client interested in evaluating adherence or persistence measures following the implementation of a refill synchronization program at independently operated community pharmacies*

**2011:** Diabetes Intensive Care Project (DICP)

*Constructed a codebook and data entry forms in Microsoft Excel for a pilot study evaluating reductions in hemoglobin A1C among indigent diabetes patients during and after regularly scheduled intensive outpatient pharmacist meeting.*

**2011:** Cost-effectiveness of fingolimod compared with first line injectable agents for multiple sclerosis.

*Description: Developed a Markov model through TreeAge evaluating the cost-effectiveness of a novel oral agent for the treatment of multiple sclerosis, incomparison with standard treatment injectable agents. This was presented in a departmental research seminar.*

**2007:** Characterization of continued antibacterial therapy after diagnosis of hospital-onset *Clostridium difficile infection*: Implications for antimicrobial stewardship

*Description: Conducted preliminary analysis and drafted report evaluating the continuation of antibacterial therapy after Clostridium difficile infection using administrative data obtained from the University HealthSystem Consortium Clinical Research Manager database of 42 hospitals, representing 5,968 patients in the final sample. Analyses were conducted using Statistical Analytical Software (SAS). First results were presented during the American College of Clinical Pharmacy annual meeting in October 2007.*

**Publications**

Harpe SE, **Inocencio TJ**, Pakyz AL, Oinonen MJ, Polk RE. Characterization of Continued Antibacterial Therapy After Diagnosis of Hospital-Onset Clostridium difficile Infection: Implications for Antimicrobial Stewardship. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*. 2012;32:744-754.

**Poster Presentations**

**Inocencio TJ**, Seetasith A, Newland A, Bose P, Holdford D. Cost-utility analysis of nilotinib compared to imatinib for newly diagnosed chronic myeloid leukemia (CML) in chronic phase. Annual meeting, ISPOR, Washington, DC. June 2012

**Inocencio TJ**, Harpe SE, Pakyz AL, Oinonen M, Polk RER. Characterization of continued use of antimicrobial therapy post-diagnosis of Clostridium difficille Associated Diarrhea (CDAD). Annual meeting, ACCP, Denver, CO. October 2007

**Inocencio TJ**, Robles JR, Kansal S, Polk RE. Predicting antibiotic resistance in nosocomially acquired Pseudomonas aeruginosa bacteremia. Annual meeting, ACCP, Denver, CO. October 2007. (Preliminary report)

**Skills and Knowledge**

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|---|---|
| Pharmacoeconomics: | Experience with decision tree and Markov modeling techniques to evaluate cost effectiveness of medical interventions. |
| Pharmacoepidemiology: | Experience with the application of adherence measures and knowledgeable regarding basic pharmacoepidemiologic principles when estimating treatment effects. |
| Statistics: | Knowledgeable with the application of various model-building and statistical and econometric techniques. |
| Databases: | HCUP National Inpatient Sample (NIS)<br>HCUP National Emergency Department Sample (NEDS)<br>National Vital Statistics System (NVSS) Multiple Cause Mortality File<br>Veterans Health Administration Medical SAS datasets<br>National Ambulatory Care System (NAMCS)<br>National Hospital Ambulatory Care System (NHAMCS)<br>Medical Expenditure Panel Survey (MEPS) |
| Pharmacotherapy: | Experience with the application clinical knowledge attained during didactic coursework to a wide array of areas during rotation experiences. |
| Analytical Software: | Statistical Analytical Software (SAS), Statistical Package for the Social Sciences (SPSS), STATA, Microsoft Excel, TreeAge |

**Clinical Rotation Experiences**

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| Hospital Pharmacy: | Preceptor: Mary Scott Garrett, RPh<br>Henrico Doctors Hospital, Parham Campus |
| Critical Care: | Preceptor: David Wyatt, PharmD<br>Henrico Doctors Hospital, Forest Campus |
| Pediatric Psychiatry: | Preceptor: Sandra Mullen, PharmD<br>Virginia Commonwealth University Medical Center |
| Oncology: | Preceptor: Ashley Newland, PharmD<br>Virginia Commonwealth University Medical Center |
| Ambulatory Care: | Preceptors: Sallie Mayer, PharmD, and Evan Sisson, PharmD<br>CrossOver Clinic and Center for High Blood Pressure |
| Advanced Community: | Preceptor: Patricia Slattum, PharmD, PhD<br>Imperial Plaza Assisted Living Facility |

**Honors**

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|---|---|
| 2012: | Phi Kappa Phi |
| 2008: | Rho Chi Honor Society, Lambda Chapter |
| 2004 - 2006: | 4.0 Grade Point Average (Undergraduate) |
| 2004: | Dean's Scholarship |

**Leadership**

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|---|---|
| 2008 - 2009: | President<br>Rho Chi Honor Society, Lambda Chapter |
| 2006 - 2008: | Secretary<br>Kappa Psi Pharmaceutical Fraternity, Theta Chapter |

**Organizations**

International Society for Pharmacoeconomics and Outcomes Research (ISPOR)

**Languages**

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|---|---|
| Primary Language: | English |
| Others: | Spanish, Filipino |